Color Atlas of Oral Cancer

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Foreword

V Shantha

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Color Atlas of Oral Cancer

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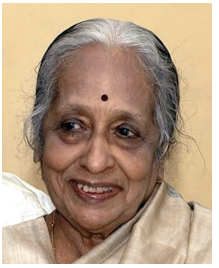
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Dedicated to

Dr V Shantha, Chairman,
Cancer Institute (WIA), Adyar, Chennai,
Tamil Nadu: a living legend in the field of oncology

Foreword



Member -WHO Advisory Committee on Cancer
Convener - State Advisory Board on Cancer
Chairman - INDO-US Collaborative Group on Lymphoid Neoplasias (Indian Chapter)
Member - many ICMR Committees
Member - ICMR Task Force on Registries
Member - Syndicate of the Anna University
President - Indian Society of Oncology (88-90)
President - Asian and Pacific Federation of Organisations for Cancer Control (97-99)
President - 15th Asian Pacific Cancer Conference (1999)
Hon. Member - International Association of Cancer Registry (IARC)

Recipient of the National Award
Padma Shri (1986)

DSc (Honoris Causa) from
Shri Venkateswara University,
Tirupati (1998)

D Sc (Honoris Causa) from
Tamil Nadu Dr MGR University (2002)
Nazli-Gad-El-Mawla Award instituted by the International Network for Cancer Treatment and Research, Brussels 2002

Ramon Magsaysay Award for
Public Service 2005

Padma Bhushan in 2006
Mother Teresa Memorial Award in 2013

The *Color Atlas of Oral Cancer* compiled by Dr Masthan, Dr Vidyarani and Dr Aravindha has attempted to provide comprehensive information to oral health experts and planners on precancer, cancer epidemiology, management and need for screening and prevention in oral cancers.

Mouth/oral cancer occupied the third rank in men and women in 1982. Today, there is a tendency for mouth cancer to go up in men, whereas it is coming down in women.

The average increase in men is 1% annually and decrease in women is 1.5%.

Our field study has documented a lower tobacco chewing habits in the higher socioeconomic and high educational population. The downward trend in chewing habit in women is directly related to education and income and is reflected in the oral cancer incidence.

The association of tobacco with oral cancer is incontrovertibly proven.

Tobacco-related oral cancer is invariably low grade squamous cell carcinoma, essentially loco regional with a fairly long evolutionary period of

precancerous changes (10–15 years), and easily identifiable at every stage. It is propensity to disseminate is minimal.

The mouth is an accessible site for diagnosis and does not need any sophisticated technology.

Since oral carcinogenesis has in general a long latency and evolves through multiple stages of precancer, primary and secondary prevention are possible and ideal.

Our field studies showed that the relative risk of oral cancer in heavy chewers is 61 times that of nontobacco users. The finding also suggested the possible existence of host factors in oral carcinogenesis.

Prevention of Oral Cancer

As in any disease, prevention is better than cure. In oral cancer control, anti-tobacco and educational awareness programs and screening play an important role and can be very cost-effective.

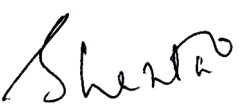
The oral pathologist has a major role in primary and secondary prevention of oral cancer.

A large percentage of the population has a dental consultation at some part of their lives. It will be necessary for all those who have an opportunity to see the oral cavity to check not only about oral and dental hygiene but also the habits they indulge in.

The dental surgeon is the primary care physician for oral cancer detection and prevention. He has a major role for primary prevention of oral cancer. Every dental surgeon should not only counsel on oral and dental hygiene but about hazards and risk factors for oral cancer — use of tobacco.

Thus, the pivotal role of a dental surgeon both for primary and secondary prevention needs no reiteration. There should be minimal delay if there is a suspicion of cancer. There should be no medical component in delay.

Oral cancer is preventable and curable if detected early.



V Shantha
MD, DGO, DSc (Honoris Causa)
Chairman
Cancer Institute (Women's India Associated), Adyar
Chennai, Tamil Nadu, India

Preface

In India, Oral Cancer prevalance ranks first among men and fourth among women. Increased incidence rates of Oral Squamous Cell Carcinoma, especially among younger generation is a major health concern. Most of the squamous cell carcinomas are preceded by the potentially malignant disorders which are treatable. Due to the ignorance of the patients and also the healthcare professionals, most of the cases are missed in the premalignant or early stage of the oral cancer. Most of the patients report to us during the late stage of the disease, resulting in the poor prognosis.

In this atlas, we have made an attempt to include all the aspects of oral squamous cell carcinoma as well as potentially malignant disorders. We have also included the photographs of etiologic agents which can serve as easy guide to convince patients for habit cessation.

Separate chapters are dedicated to the clinical presentation of these lesions and also step-by-step process of clinical examination. All the available treatment options are listed for the potentially malignant disorders with the references. In all the chapters photographic illustrations are included.

This book is brought out as an effort to create awareness among the oral healthcare professionals. We hope this book will be useful for the instant clarification of the clinical diagnosis as well as for the patient education.

With the profound sense of gratitude and respect, we express heartfelt gratitude to Padma Bhushan Dr V Shantha, Chairman, Cancer Institute (WIA), Adyar, Chennai, for giving FOREWORD in spite of her hectic schedule. We would also like to thank Dr Vijayalakshmi R, Associate Professor, Department of Preventive Oncology, Cancer Institute (WIA), Chennai, for her guidance in spite of her busy schedule.

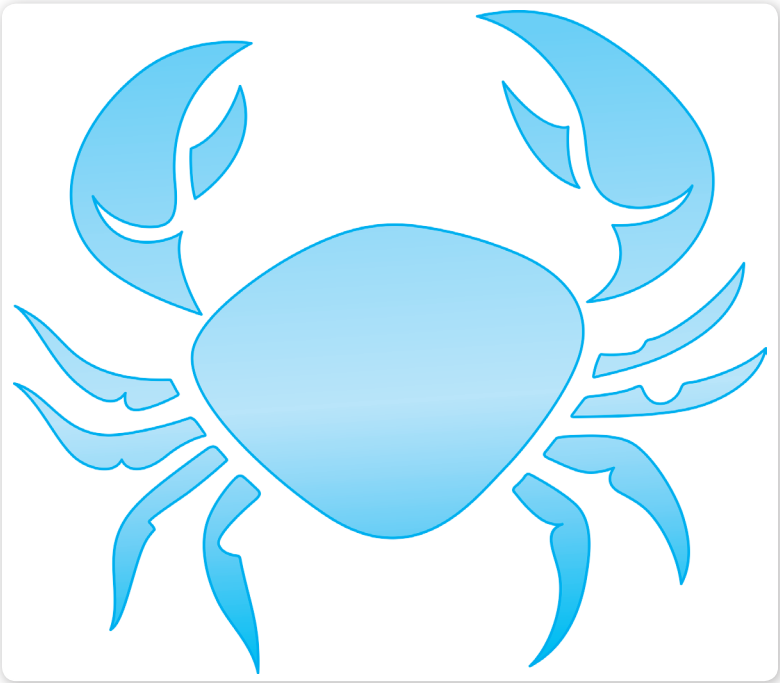
KMK Masthan
Vidyarani Shyamsundar
N Aravindha Babu

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Chapter 1

Introduction



Word “cancer” derived from the Latin word “*karkinos”,* which means crab. It is explained so because of the nature of cancerous cells which adhere to any part that they size upon in an obstinate manner like a crab. Malignant neoplasms are a broad group of diseases involving unregulated cell growth. All the malignant tumours are collectively called as cancer.

Oral cancer is a heterogeneous group of diseases arising from different parts of the oral cavity such as lip, tongue and gingiva, floor of the mouth, buccal mucosa, palate and the retromolar trigone. It is the 6th most common cancer worldwide. In India, it ranks among top three of all cancers.

The oral cancer includes several types of cancers in the oral cavity such as oral squamous cell carcinoma, malignant salivary gland tumours, melanoma, basal cell carcinoma etc. Oral squamous cell carcinoma (OSCC) constitutes to over 90% of all cancers in oral region. The word Oral cancer is used almost synonymous to oral squamous cell carcinoma.

The development of majority of OSCC appears to be due to chronic exposure to topical carcinogens, specially tobacco (smoked and smokeless), aracanut and alcohol. Carcinogenic substances alters genetic configuration of oral epithelial cells. As a result, normal oral epithelium gets converted into potentially malignant (dysplastic) lesions and subsequently to the invasive Oral squamous cell carcinoma (OSCC).

Cancer begins with multiple cumulative epigenetic and genetic alterations that sequentially transform a cell or a group of cells in a particular organ. The early genetic events might lead to clonal expansion of pre-neoplastic daughter cells in a particular tumour field. Subsequent genomic changes in some of these cells drive them towards the malignant phenotype. These transformed cells are diagnosed histopathologically as cancers owing to changes in cell morphology. Conceivably, a population of daughter cells with early genetic changes (without histopathology) remain in the organ, responsible for field cancerization. It is also noted that about 50% of oral squamous cell carcinomas arise from apparently normal appearing oral mucosa clinically.

There are multiple modifications in the physiology of cancer cell, such as unlimited replicative potential, self sufficiency of growth signals, insensitivity to growth inhibitor signals, evasion of apoptosis, ability to promote sustained angiogenesis, and capacity to invade surrounding tissue and metastasize.

Currently, numerous newer instruments for screening and advanced diagnostic aids are available. But still the histopathological diagnosis following the biopsy is the gold standard in the diagnosis of potentially malignant disorders and malignancy.

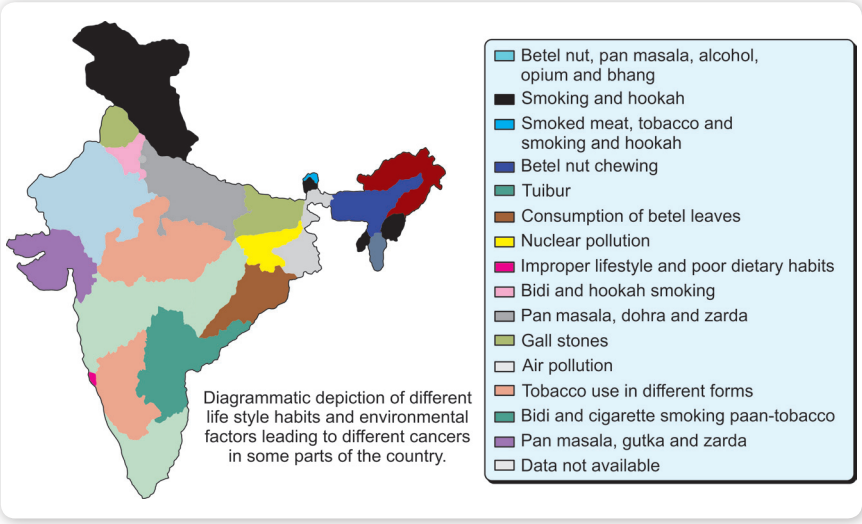
Even though numerous markers are available currently, none of the available molecular markers have proved to be of diagnostic or prognostically significant. All these lesions can be easily visualised. Early diagnosis and prevention of malignant transformation of potentially malignant lesions are the best way to improve the prognosis. The knowledge about the screening, the clinical appearance and management among health care providers is very important.

Chapter 2

Epidemiology

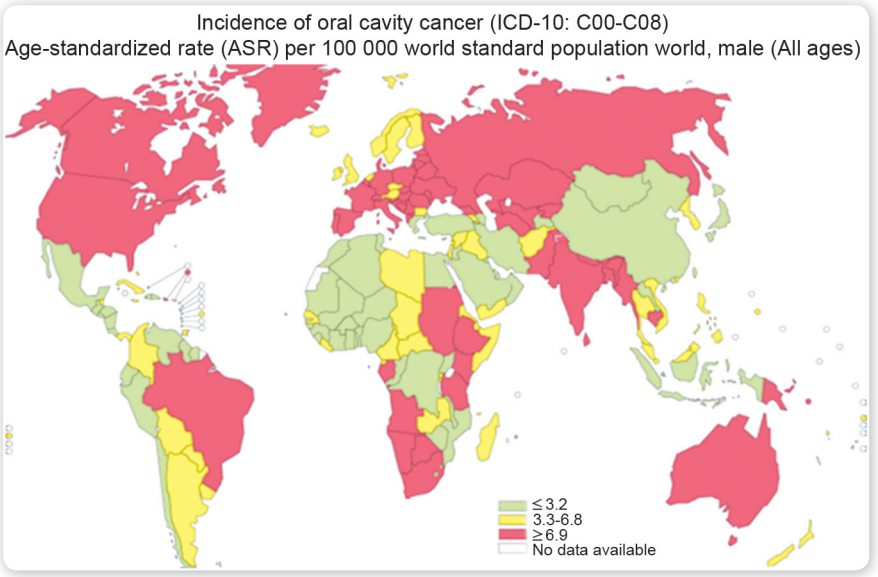
The incidence widely varies in different part of the world and ranges from approximately 2–10 per 100,000 population per year. In India, it represents 40% of all cancers and is the second most prevalent cancer in men and third most prevalent in women.

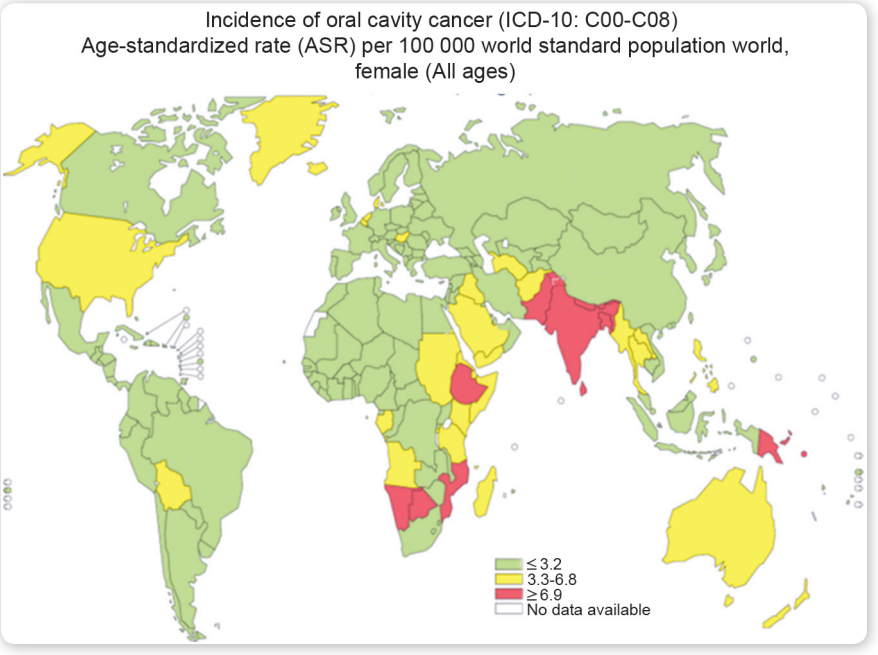
In spite of various therapeutic as well as diagnostic advances the overall incidence and mortality due to oral cancer are rising. The annual estimated incidence of oral cancer is around 275,000.



Diagrammatic depiction of different life style habits and environmental factors leading to different cancers in some parts of the country.

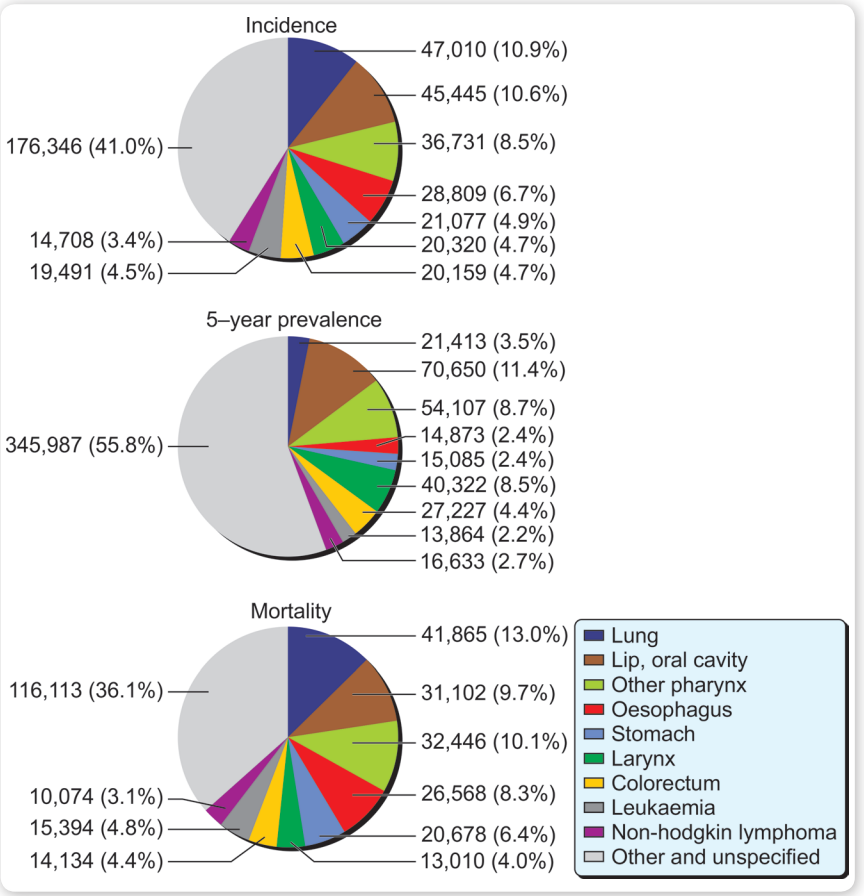
Source: Ali I, Wani WA, Saleem K. Cancer scenario in India with future perspectives. Cancer Ther. 2011;8:56-70.



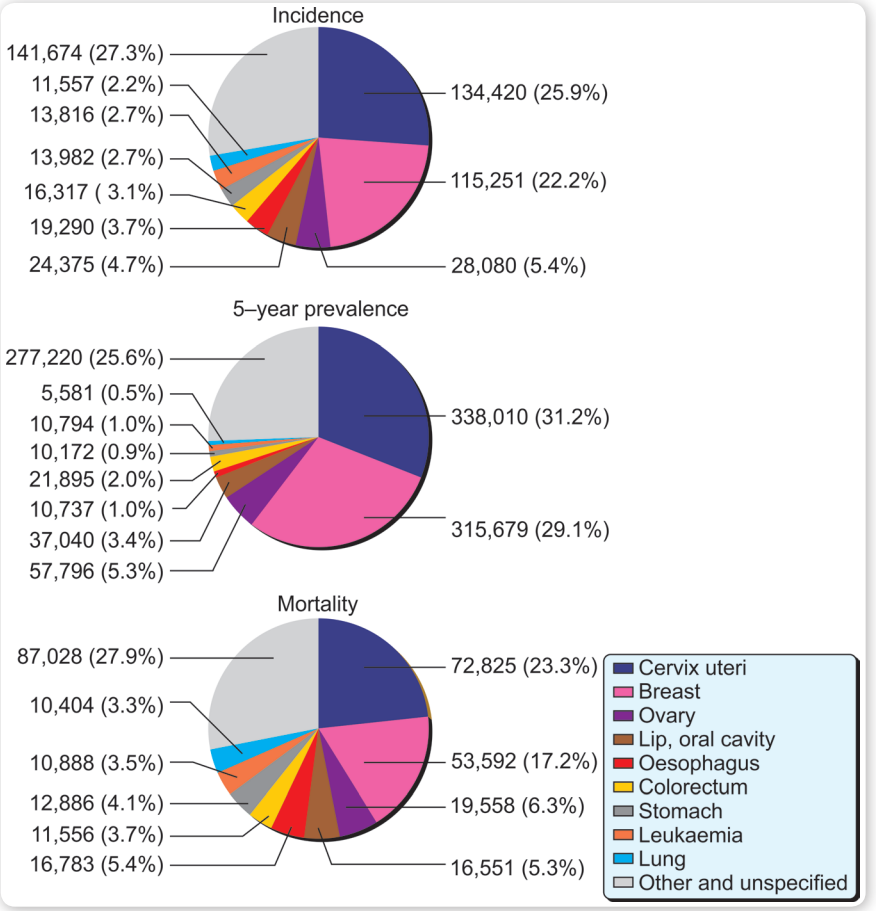


Source: GLOBOCAN 2002 International agency for research on cancer.

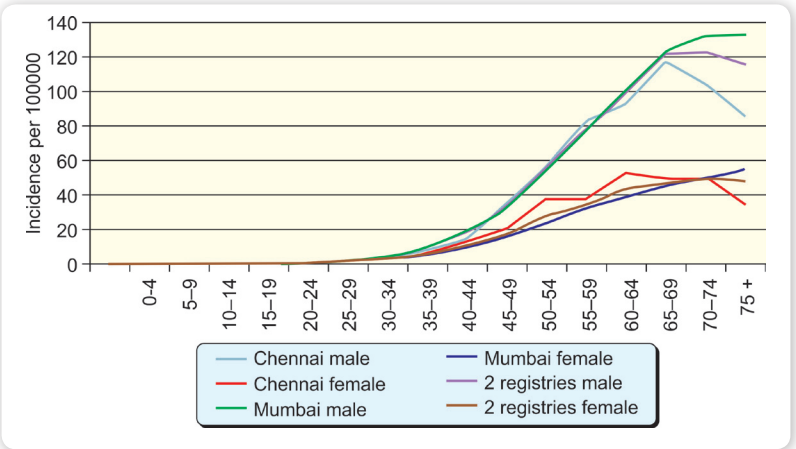
Most frequent cancers: Men in India (*Source:* Globocan 2008)



Most frequent cancers: Women In India (*Source:* Globocan 2008)

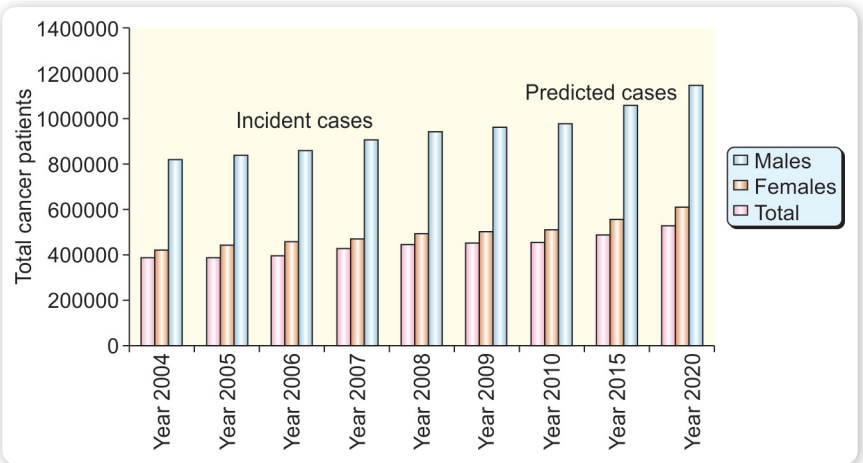


Age specific incidence rates lip, oral cavity cancer



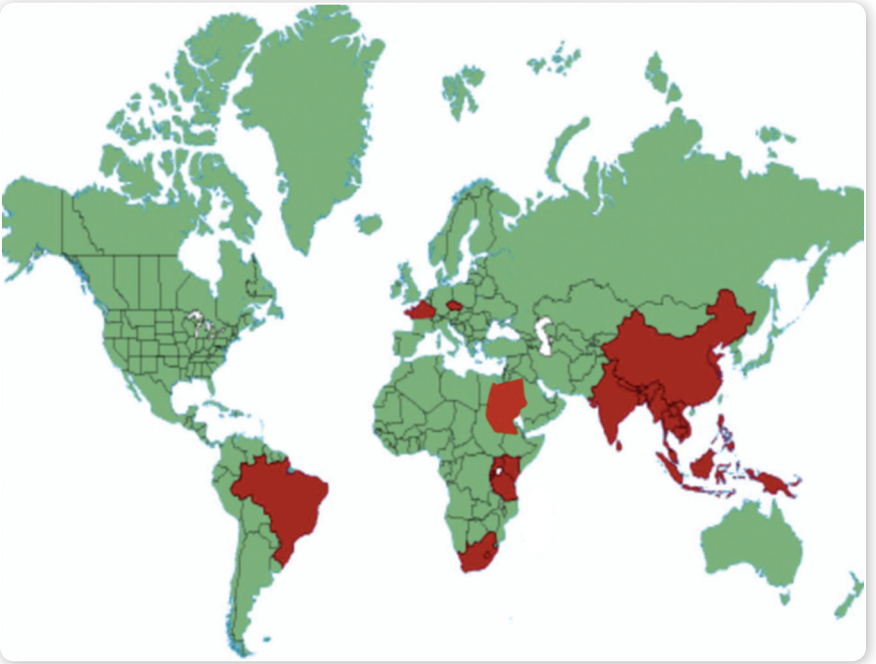
Source: Coelho KR. Challenges of the oral cancer burden in India. J Cancer Epidemiol. 2012;2012:70:1932.

Year-wise total cancer prevalence in India



Source: Ali I, Wani WA, Saleem K. Cancer scenario in India with future perspectives. Cancer Ther. 2011;8:56-70.

Countries with high incidence and mortality from oral cancer



Source: Warnakulasuriya S. Global epidemiology of oral and oropharyngeal cancer. Oral Oncol. 2009;45:309-16

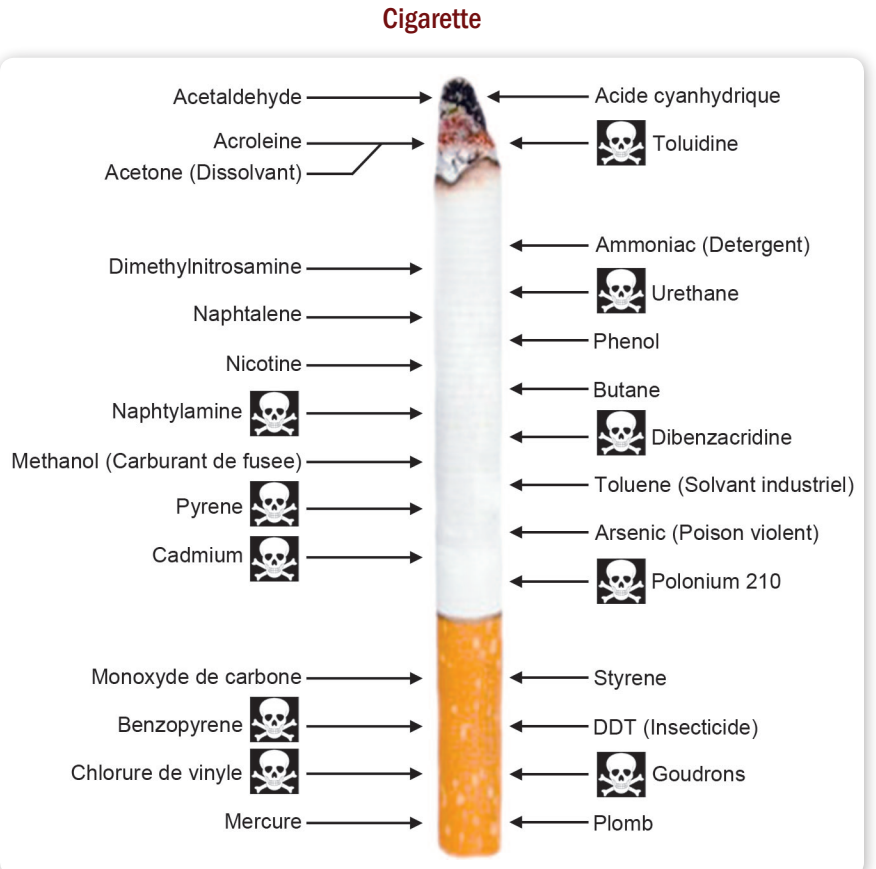
Chapter 3

Causes of Oral Potentially Malignant Disorder and Cancer

Established risk factors	*Other possible risk factors*
➢ Smoking tobacco—Cigarettes, cigars, pipes, bidis. ➢ Smoking tobacco—Chewing tobacco, oral snuff and other tobacco products. ➢ Chewing betel quid, pan, gutka and pan masala containing areca nut. ➢ High alcohol consumption. ➢ The presence of potentially malignant oral disorders (e.g. lichen planus). ➢ Excessive exposure to sunlight or radiation (for lip cancer). ➢ Age, in conjunction with other risks related.	➢ Diet lacking in fruits and vegetables. ➢ Viral infections e.g. certain type of human papilloma virus (HPV) particularly for oropharyngeal cancers. ➢ Immune deficiency disease or immune suppression. ➢ Mate drinking (particularly as a hot beverage). ➢ Chronic sepsis in the mouth (especially in those with major risk factors).

Source: Warnakulasuriya S. Global epidemiology of oral and oropharyngeal cancer. Oral Oncol. 2009;45:309–16.

DIFFERENT FORMS OF TOBACCO SMOKING

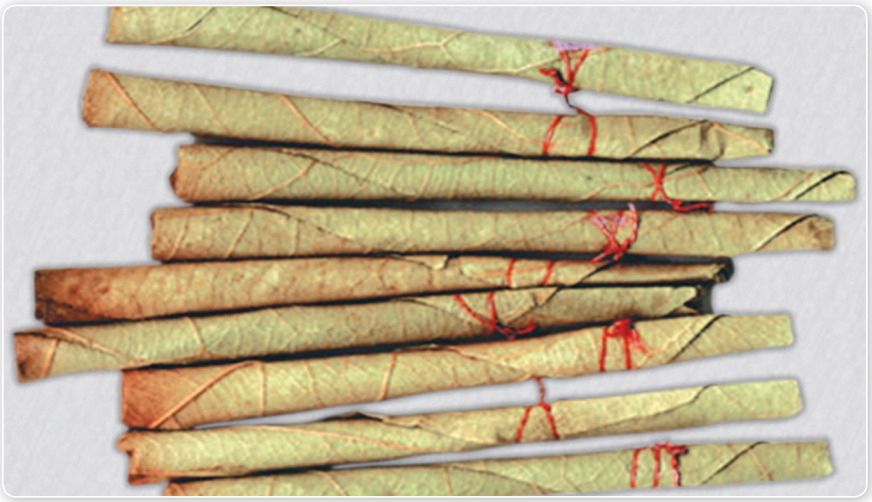


Cigarette consisting mainly of a tobacco blend, paper, PVA glue to bond the outer layer of paper together, and often also a cellulose acetate-based filter.

Source: http://www.smokernewsworld.com and http://www.darkgovernment.com

Bidi





A thin, Indian cigarette filled with tobacco flake and wrapped in a Tendu or even *Bauhinia racemosa* leaf tied with a string at one end.

Source: (http://www.topnews.in, and en.wikipedia.org).

Cigar





Tightly-rolled bundle of dried and fermented tobacco.

Source: http://www.nytimes.com&http://en.wikipedia.org

Roll your own (RYO)



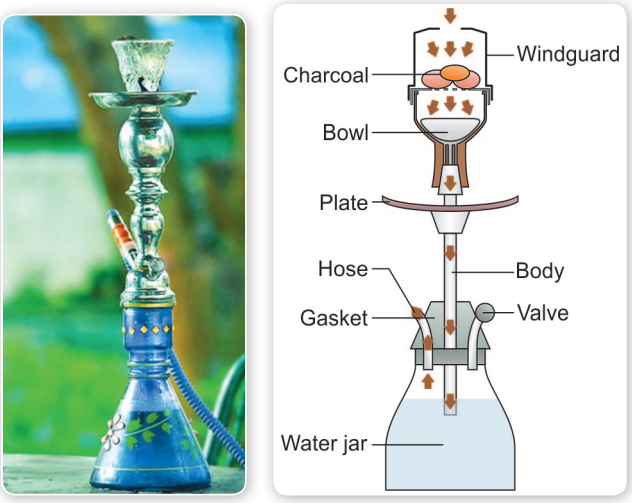
A cigarette made from loose tobacco and rolling papers.

Source: http://www.gasp.org.uk, http://en.wikipedia.org

Reverse smoking



Mu'assel/Hookah



A syrupy tobacco mix with molasses and vegetable glycerol as moisturizer and specific flavors added to it.

Source: http://en.wikipedia.org

CHEWABLE FORMS OF TOBACCO

Gutka



A preparation of crushed betel nut, tobacco, and sweet or savory flavorings.

Source: http://en.wikipedia.org, http://www.medindia.net.

Betel quid



Composition of betel quid: Betel leaves (A) with slaked lime (B), areca nut (C) and tobacco (D).

Source: http://screening.iarc.fr

Khaini





Ingredients: Tobacco, lime, water menthol, oil, spices contains added flavors.

Source: http://chainikhaini.com/, http://www.indianexpress.com

OTHER FORMS OF TOBACCO

Creamy Snuff



Consisting of tobacco, clove oil, glycerin, spearmint, menthol, and camphor, and sold in a tooth paste tube.

Source: http://en.wikipedia.org&http://lifeonthecurb.com.

Snuff



Made from a variety of ground or pulverized tobacco leaves, it is insufflated (inhaled) or "snuffed" into each nostril.

Snus



The ground tobacco is mixed with water, salt, and an alkylizing agent (sodium carbonate) and aroma.

Source: http://en.wikipedia.org,http://science.howstuffworks.com.

Alcohol



Alcohol misuse

Areca nut

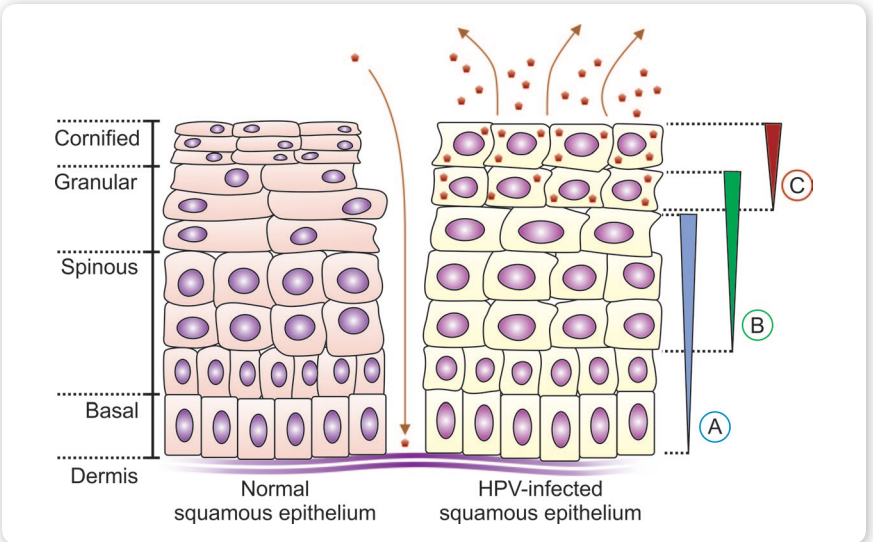




Chronic trauma from sharp tooth



Human papillomavirus



A: Early gene expression E1, E2, E6 and E7; B: Viral genome amplification; C: Virion assembly and release.

Source: Soave DF, et al. The role of human papillomavirus in precancerous Lesions and Oral Cancers.

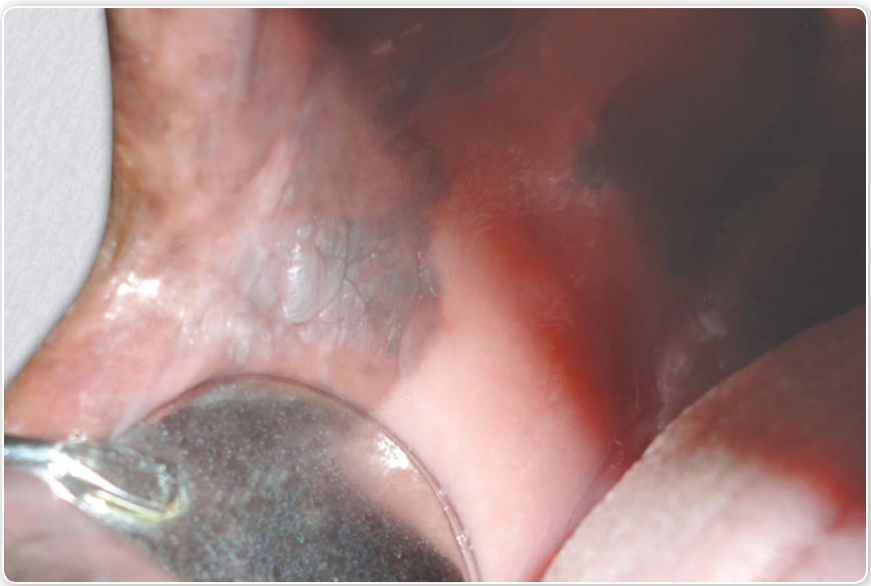
High risk groups are HPV 16 and 18. The viral genetic material integrates with the human genome. The possible mechanism of carcinogenesis is the inactivation of host tumor suppressor genes.

Chapter 4

Clinical Features of Oral Potentially Malignant Disorders

CLINICAL VARIANTS OF LEUKOPLAKIA

Homogenous Leukoplakia



Homogenous thin leukoplakia.



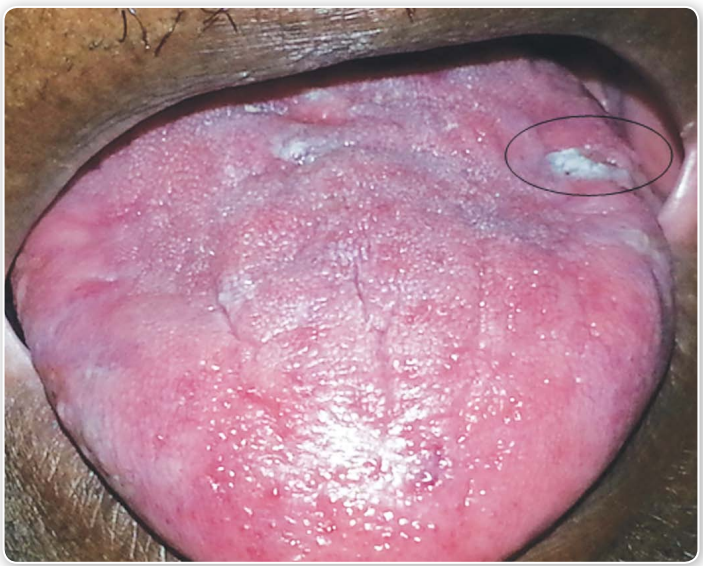
Thick leukoplakia on the buccal mucosa.



Homogenous leukoplakia of the right buccal vestibule.



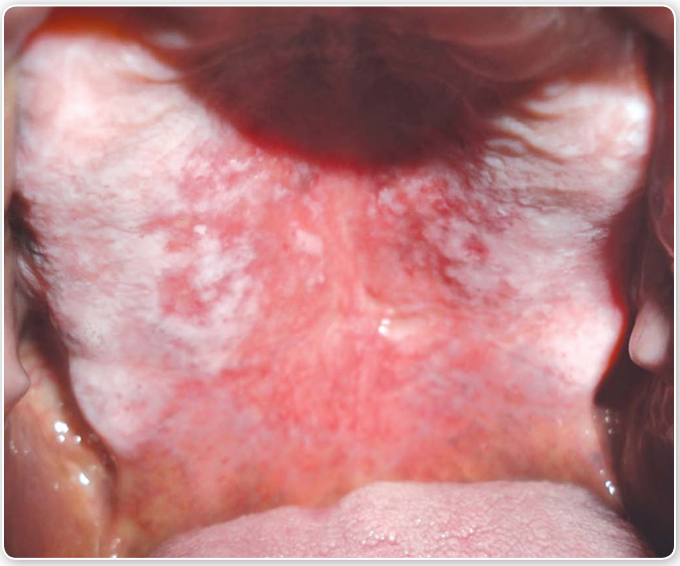
Large homogenous leukoplakia at the site of tobacco pouching.



Leukoplakia of the tongue. Patient had complain of severe dryness of the mouth.



Erythroleukoplakia—Lesion with mixed white and red areas.



Erythroleukoplakia of the palate in an edentulous patient.



Nonhomogenous leukoplakia involving angle of the mouth.



Large leukoplakia on the buccal mucosa colored red with betel quid chewing.

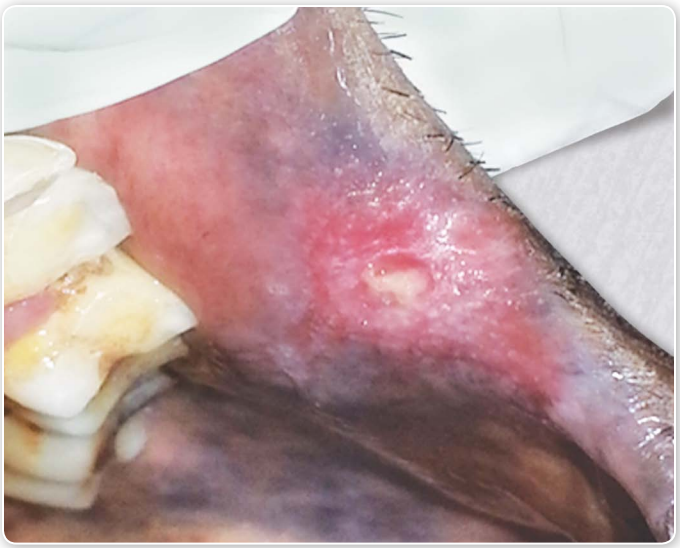


Leukoplakia of the lower lip in a bidi smoker.

Nodular Leukoplakia

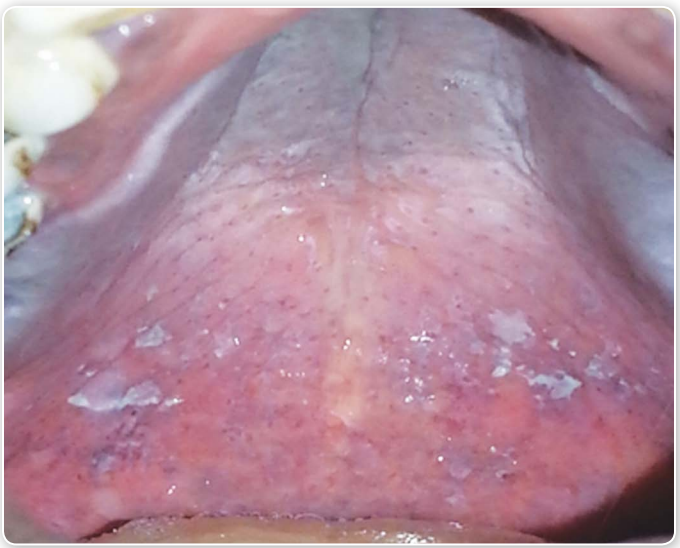


Nodular leukoplakia at the anterior buccal mucosa in a patient with the habit of tobacco chewing.



Nodular leukoplakia with the nonhealing ulcer. Biopsy showed severe dysplasia and early SCC at the region of the ulcer.

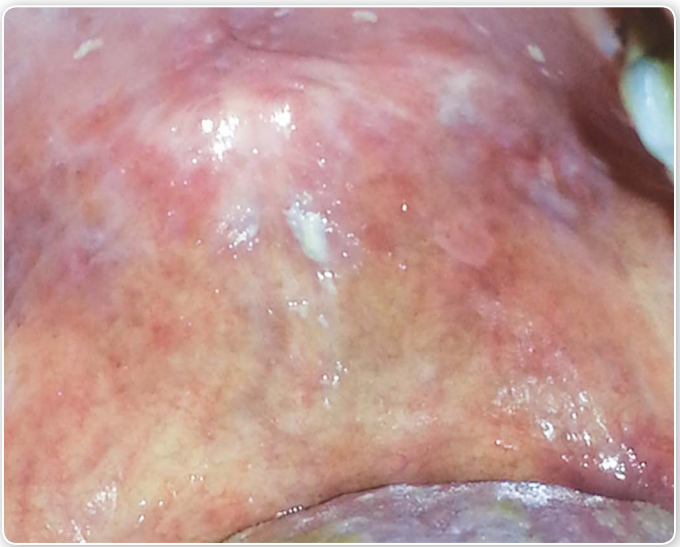
Leukoplakia of the Palate



Smokers palate with erosive areas in the soft palate. No candida hyphae were seen in a smear. Biopsy from the palate showed severe dysplasia.

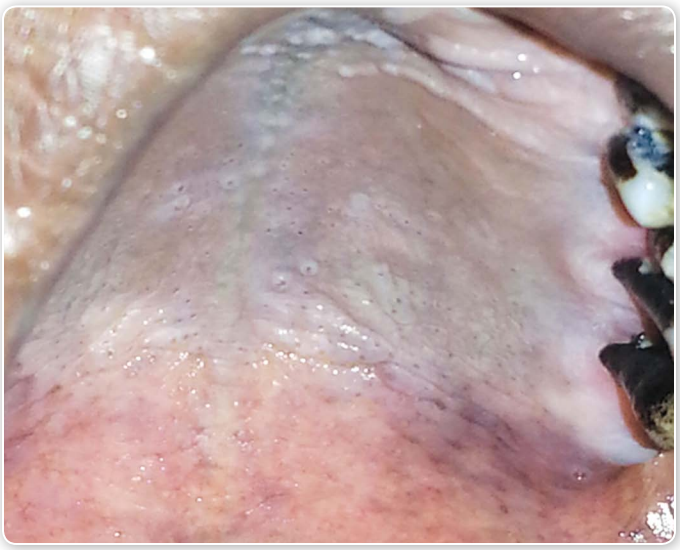


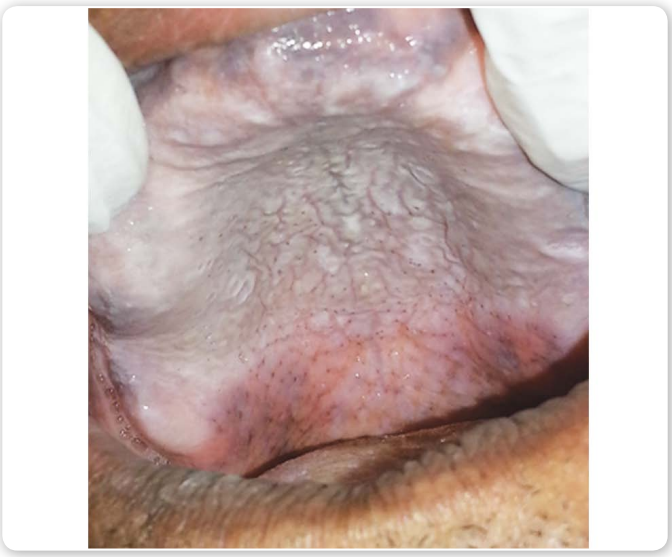
Smokers palate with erosive areas in the soft palate. No candida hyphae were seen in a smear. Biopsy from the palate showed severe dysplasia.



Pseudomembranous candidiasis of the palate. It is very important to differentiate the pseudomembranous candidiasis from the leukoplakia. Pseudomembranous candidiasis can be treated by antifungals, and not a premalignant lesion

Smokers Palate

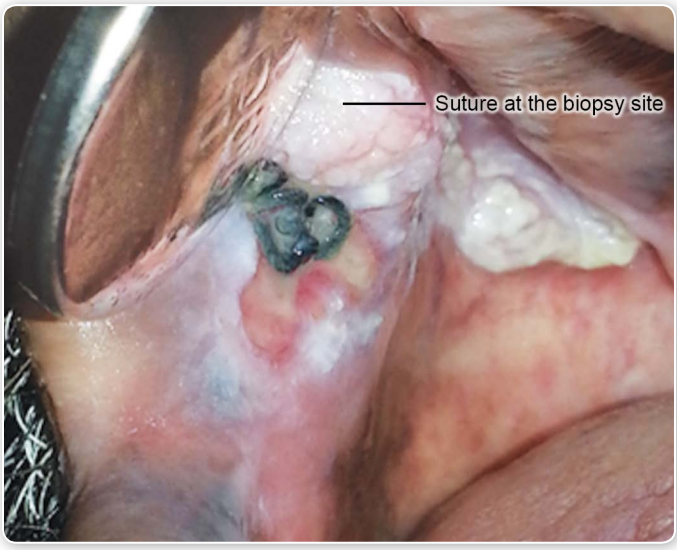




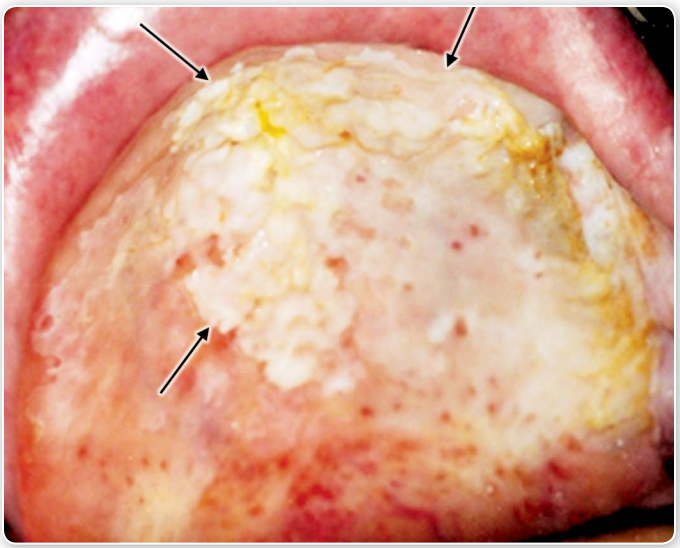
Smokers palate showing severe hyperkeratinization of the palate.



Smokers palate with erythematous areas. Biopsy from the erythematous area showed moderate dysplasia.



Proliferative verrucous leukoplakia.



Verrucous leukoplakia

Source: http://screening.iarc.fr



Tobacco pouch keratosis



Tobacco pouch keratosis



Tobacco pouch keratosis of the maxillary labial vestibule.

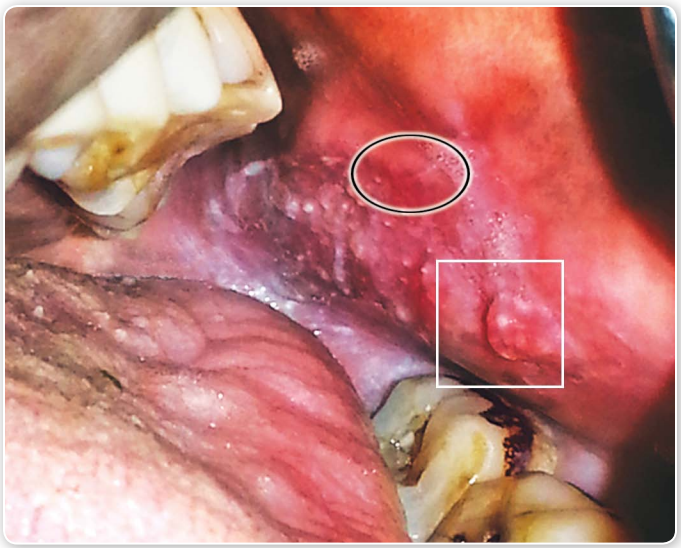


Tobacco pouch keratosis associated with the non-healing ulcer in the gingiva (within the circle). Biopsy from the nonhealing ulcer showed moderately differentiated squamous cell carcinoma.



Erythroplakia

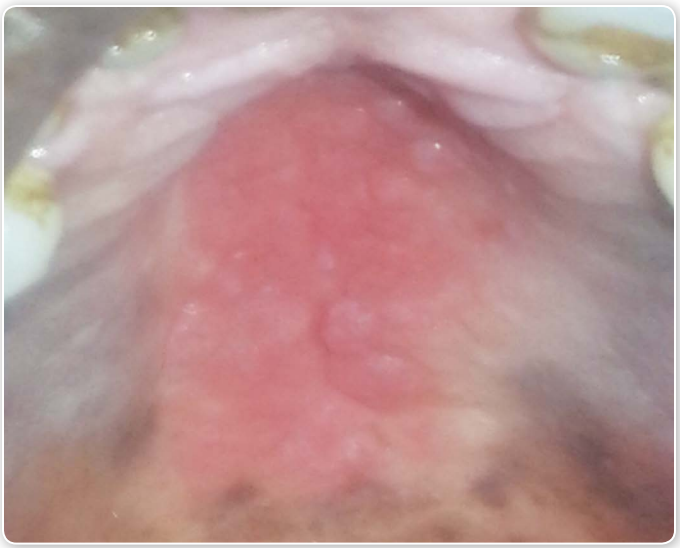
Source: http://screening.iarc.fr



Erythroplakia associated with SCC. First biopsy (from black circle) showed only moderated dysplasia. Repeat biopsy (White circle) showed moderately differentiated SCC. This explains the importance of taking biopsy from the representative site.



Chronic nonhealing ulcer in buccal mucosa of a tobacco quid chewer. Biopsy showed severe dysplasia.



Erythematous proliferative lesion on the hard palate of a bidi smoker. Biopsy showed severe dysplasia.

ORAL SUBMUCOUS FIBROSIS (OSF)



Early OSF, seen as blanching of the buccal mucosa and lips in young patient.



Early OSF, blanching of buccal mucosa is noticed.



OSF, blanching of buccal mucosa and lip mucosa.

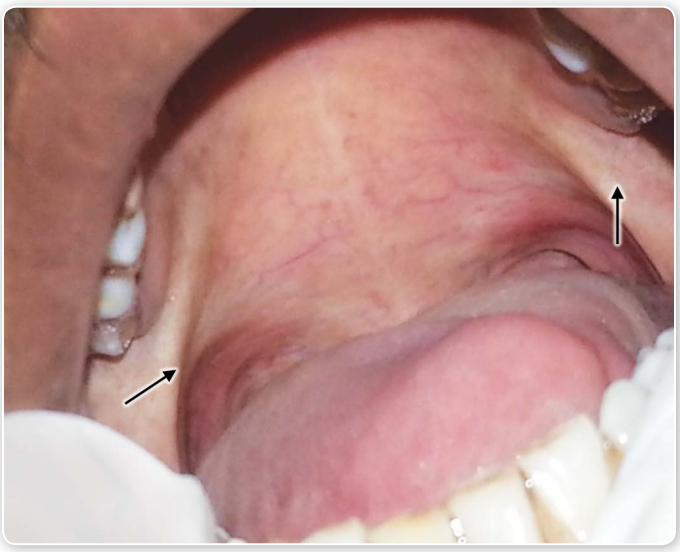


Severe OSF—Fibrous bands can be visualized on the right buccal mucosa.

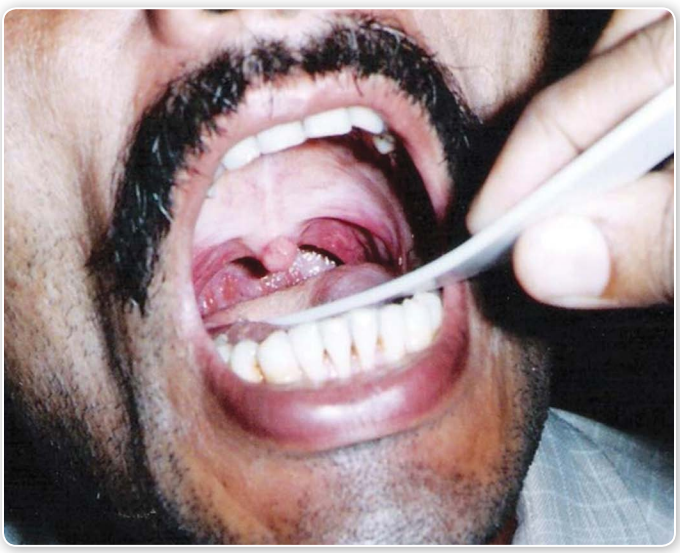
Severe Fibrosis of the Soft Palate



Severe fibrosis of the buccal mucosa (black arrow) and the pterygomandibular raphae (white arrow).



Moderate OSF—very prominent, fibrosed pterygomandibular raphae.



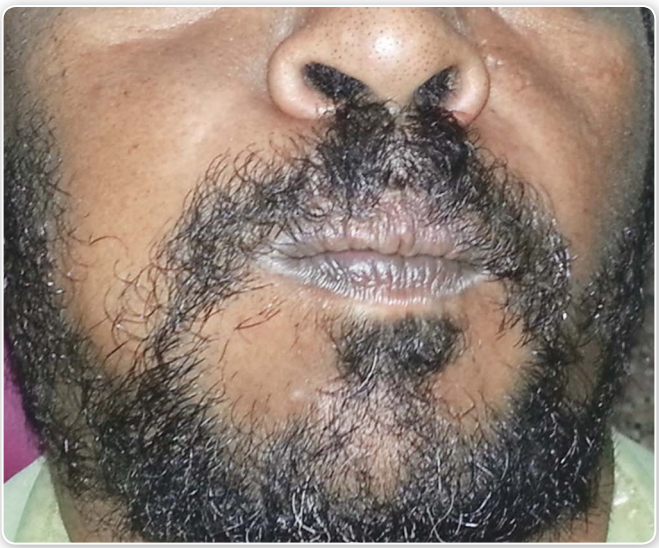
Severe oral submucous fibrosis involving the hard and soft palate.



Severe fibrosis of the soft palate.



Mild OSF. Small homogenous leukoplakia seen on the buccal mucosa.



Inability to fill air in the cheek due to OSF.



Moderate OSF with the blanching of the ventral surface of the tongue and floor of the mouth. Tiny bleeding spots are seen on the ventral surface of the tongue.

http://dentalebooks.com



Moderate OSF. Erythroplakia (within circle) seen on the posterior buccal mucosa.

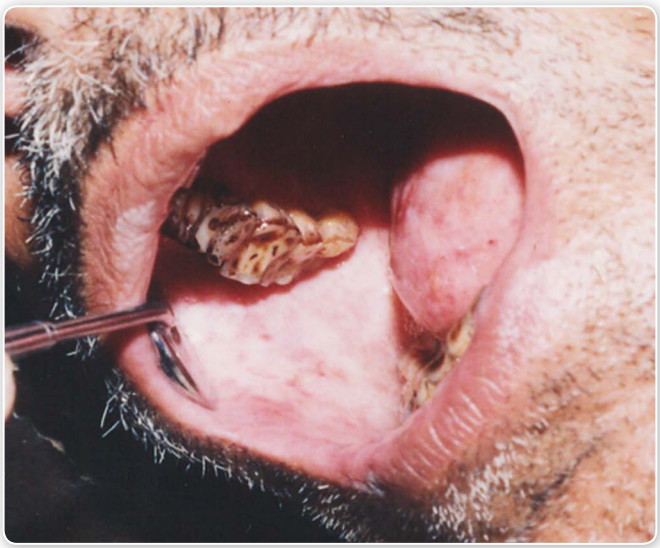


OSF with moderately restricted mouth opening.

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Same as above patient-OSF with malignant ulcer in the buccal mucosa.

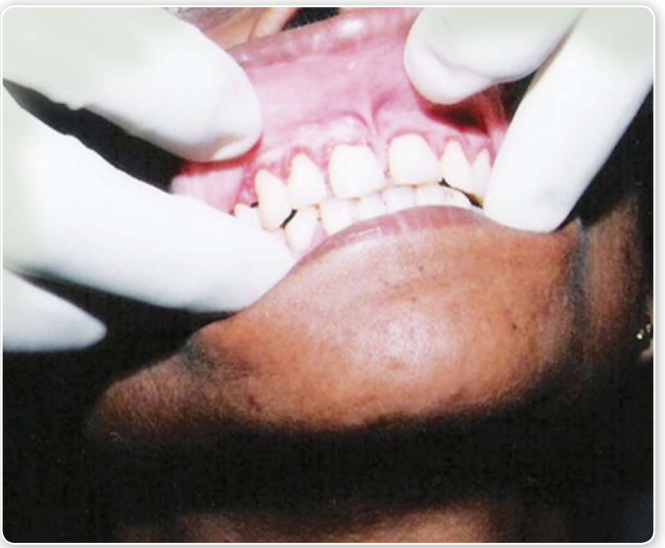


Extreme blanching of buccal mucosa and bald tongue.

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Blanching of gingiva and labial mucosa.



Blanching of gingiva and labial mucosa.

http://dentalebooks.com



Blanching of lower lip.



Blanching seen in the ventral surface of the tongue.

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Mouth Opening

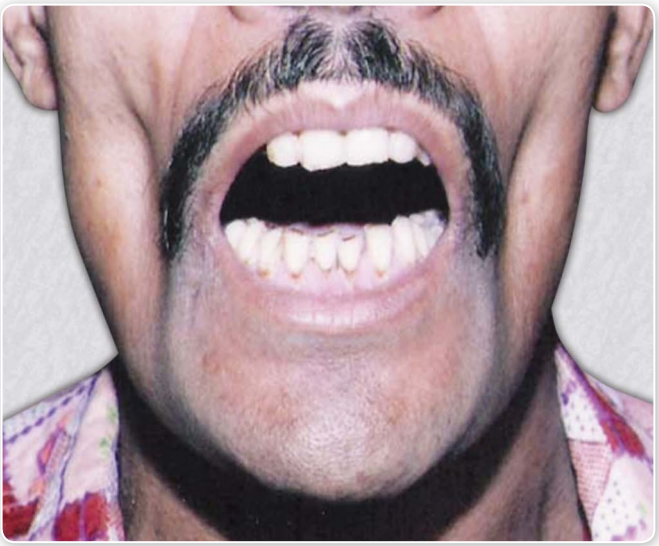


Mild reduction of mouth opening in early OSF.

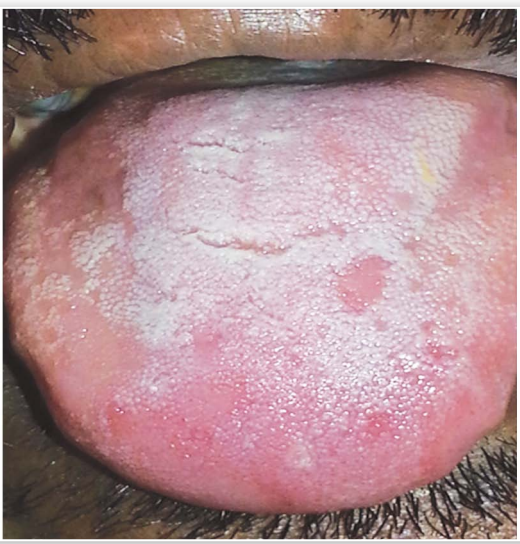


OSF with moderate reduction in mouth opening.

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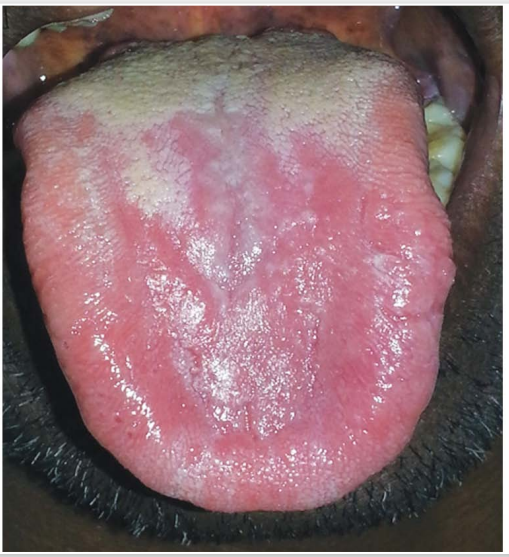


Severe OSF with restricted mouth opening.

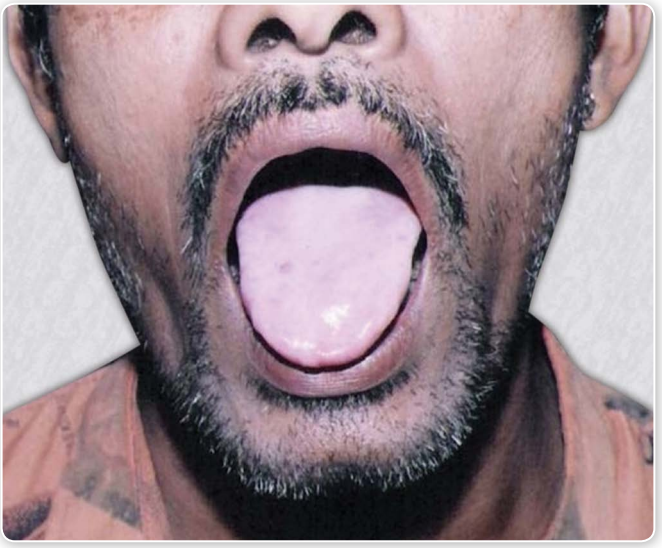


Patchy depapillation of the tongue .

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Partial depapillation of the tongue in OSF.



Bald tongue due to depapillation.

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Bald tongue due to depapillation and tiny vesiculations.



Bald tongue with vesicle (black arrow) and nonhealing ulcer (white arrows) in an edentulous patient.

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Blanching of the ventral surface of the tongue in OSF patients.



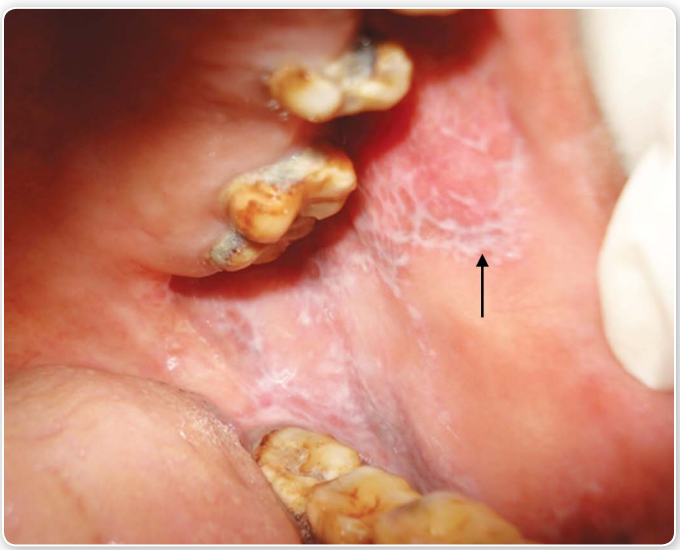
Restricted movement of the tongue, demonstrated by inability of the tip of the tongue to touch the anterior hard palate.

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Actinic chelitis.

LICHEN PLANUS



Reticular lichen planus of the buccal mucosa
(Arrow: showing Wickham's striae).

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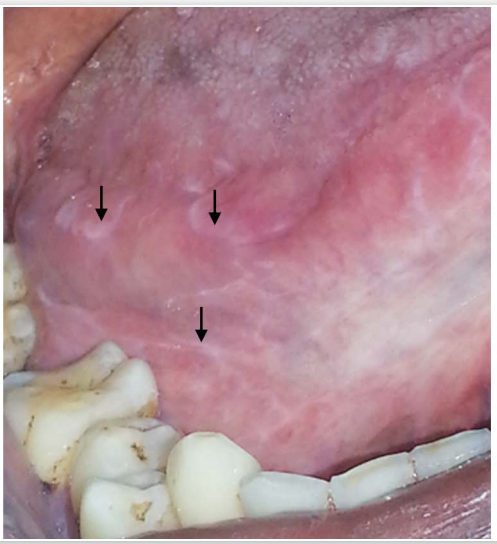


Reticular lichen planus: white striations are Wickham's striae, and the pigmentation seen due to healing.

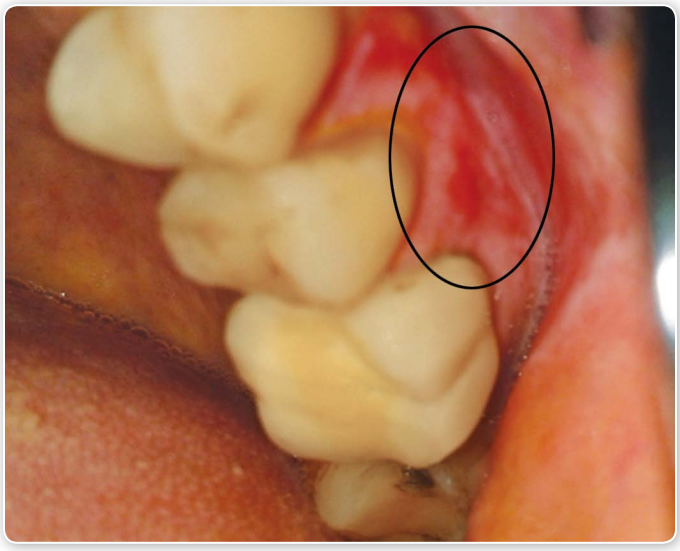


Reticular lichen planus of the labial mucosa.

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Reticular lichen planus of the tongue (Arrows showing Wickham's striae).



Erosive lichen planus of the maxillary gingiva.

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Erosive lichen planus seen on the right cheek.

Approximate malignant transformation potential malignant lesions and conditions

Approximate malignant potential	*Lesion*	*Known etiological factors*	*Main features*
Very high (85%+)	Erythroplasia	Tobacco/alcohol	Red plaque
High in some instances	Actinic cheilitis	Sunlight	White plaque/ erosions
30%+	Chronic candidiasis Candidal (leukoplakia)	Candida albicans	White or speckled white and red plaque
	Dyskeratosis congenita	Genetic	White plaques
	Leukoplakia (non-homogeneous)	Tobacco/alcohol	Speckled white and red plaque or nodular plaque
	Proliferative verrucous leukoplakia	Human papillomavirus (HPV): most often no history of tobacco/alcohol	White or speckled white and red or nodular plaque

Contd...

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Contd...

	Sublingual keratosis	Tobacco/alcohol	White plaque
	Submucous fibrosis	Areca nut	Immobile pale mucosa
	Syphilitic leukoplakia	Treponema pallidum	White plaque
Low (< 5%)	Atypia in immunocompromised patients	HPV	White or speckled white and red plaque
	Leukoplakia (homogeneous)	Friction/tobacco/alcohol	White plaque
	Discoid lumps erythematosis	Autoimmune	White/plaque/erosions
	Lichen planus	Idiopathic	White/plaque/erosions
	Fanconi syndrome	Genetic; anemia	White plaques
	Paterson-Kelly-Brown syndrome (sideropenic dysphagia; Plummer-Vinson syndrome)	Iron deficiency	Post-cricoid web

Source: Scully G, Bagan JV, Hopper C, Epstein JB . Oral cancer: current and future diagnostic techniques. Am J Dent. 2008;21:199-209.

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Chapter 5

Clinical Presentation of Oral Squamous Cell Carcinoma (SCC)



SCC of the buccal mucosa fungating extra orally.

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SCC presenting as fungating mass involving the upper lip and part of lower lip.



SCC of the lower labial sulcus with extensive destruction of the lower lip.

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SCC of the tongue presenting as proliferative lesion.



SCC involving posterior one–third of the tongue.

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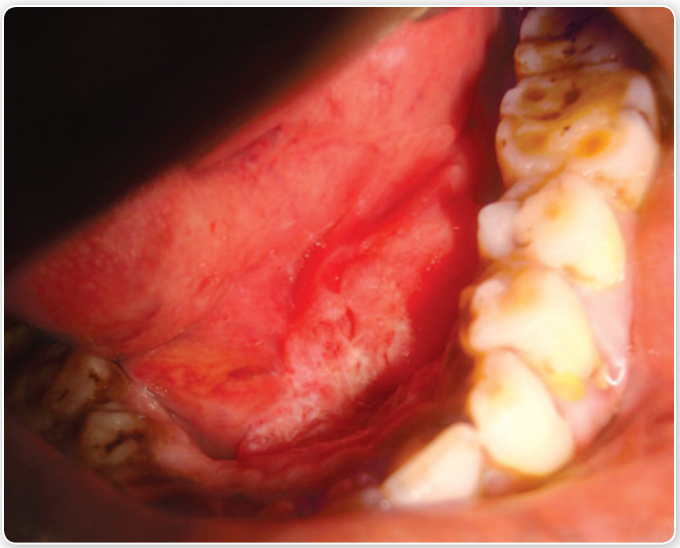


SCC of lateral border of the tongue, due to trauma from sharp third molar tooth.

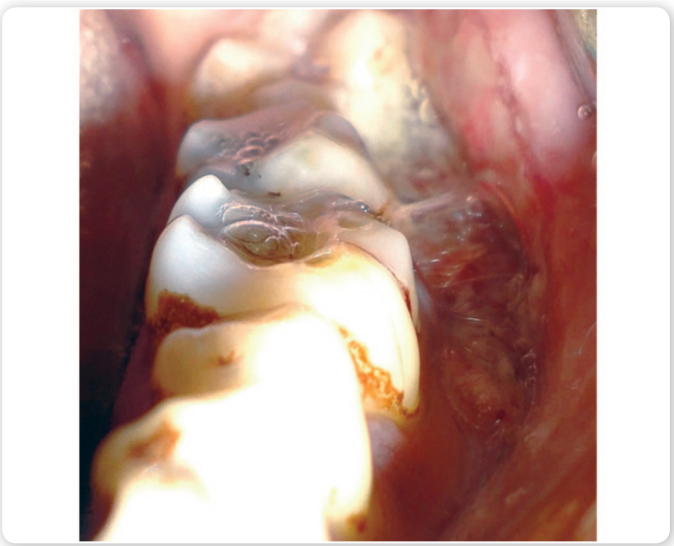


Biopsy from the leukoplakia showed mild dysplasia (white arrow) and the erythematous area (black arrow) showed moderately differentiated SCC.

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SCC of the floor of the mouth.

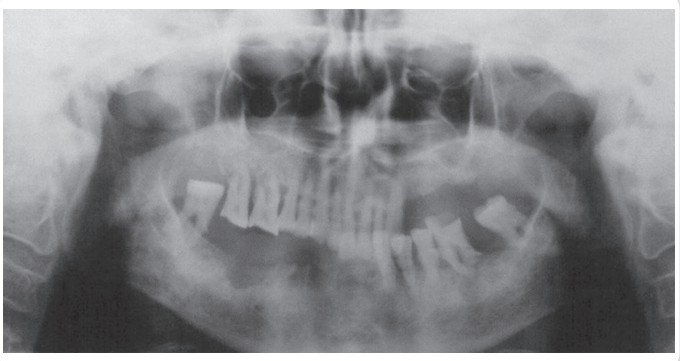


SCC of the mandibular buccal sulcus presenting as a nonhealing ulcer.

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SCC involving the mandibular alveolus, presenting as an ulceroproliferative lesion.

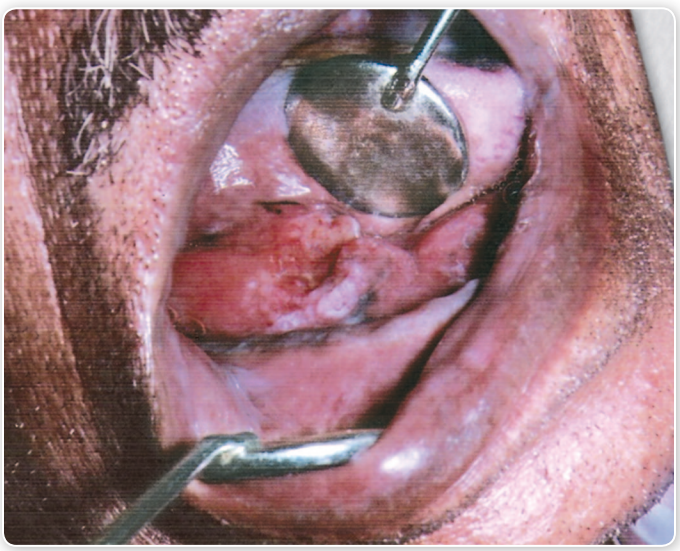


Orthopantomograph of the above patient showing destruction of the mandibular bone.

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SCC of the mandibular alveolus presenting as extensive ulcer.

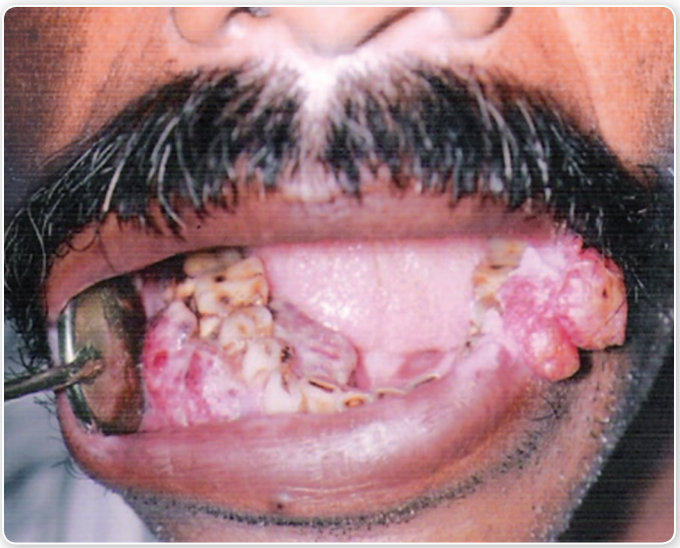


SCC of the edentulous alveolus and floor of mouth.

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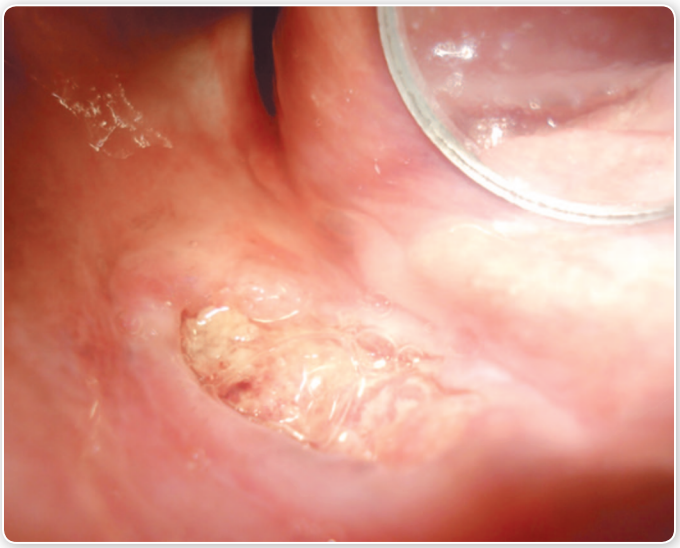


SCC presenting as a proliferative lesion.

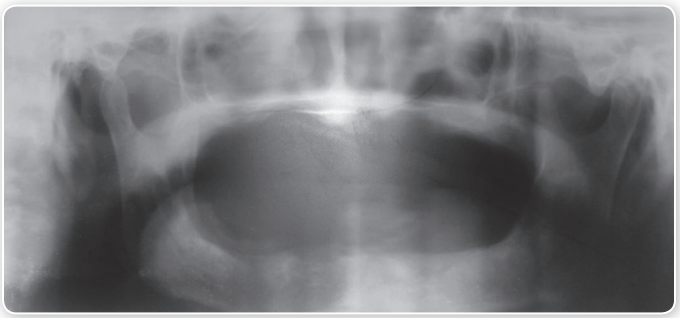


Bilateral SCC.

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SCC of the edentulous alveolus with the exposure of the bone.

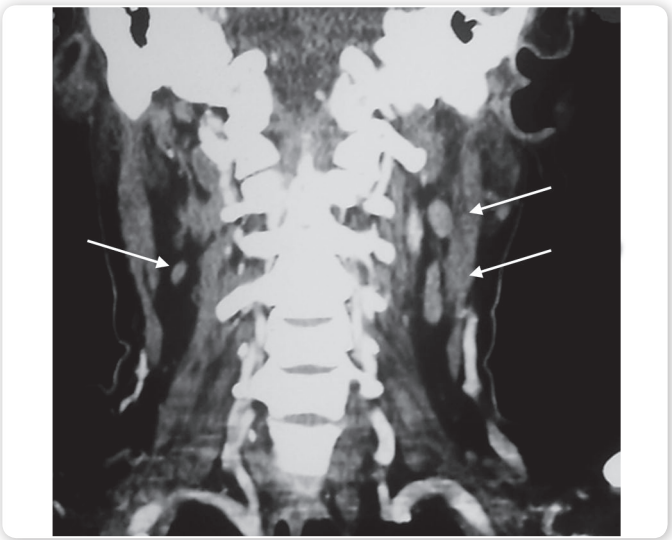


OPG of the above case showing ill-defined radiolucency of the bone.

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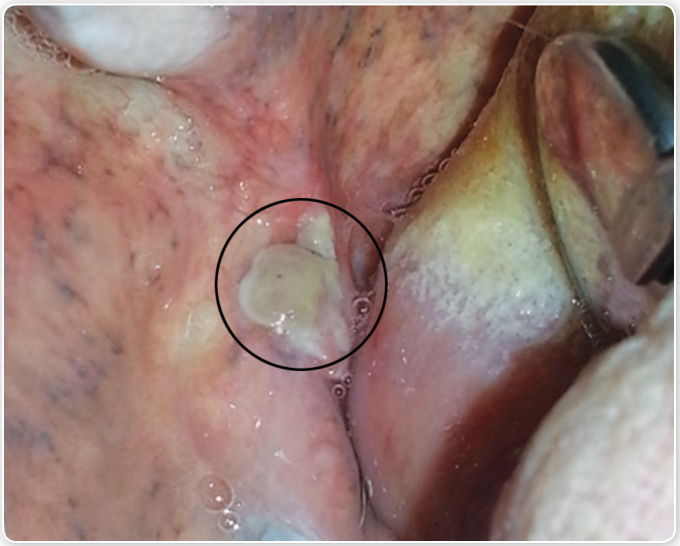


Squamous cell carcinoma of the retromolar region.



CT of the above patient showing few enlarged lymph nodes.

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Ulceroproliferative lesion at the retromolar region in a bidi smoker. Biopsy showed poorly differentiated SCC.

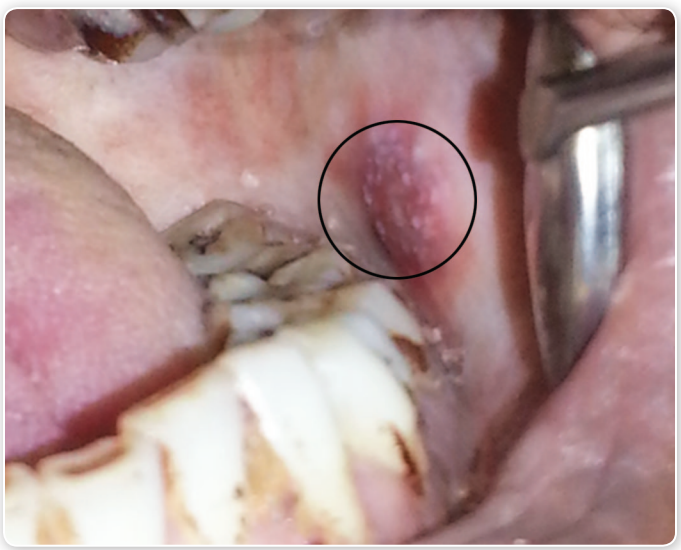


Squamous cell carcinoma presenting as a small erosive area in the hard palate.

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Erythematous lesion on the hard palate of a bidi smoker. Biopsy showed well-differentiated SCC.

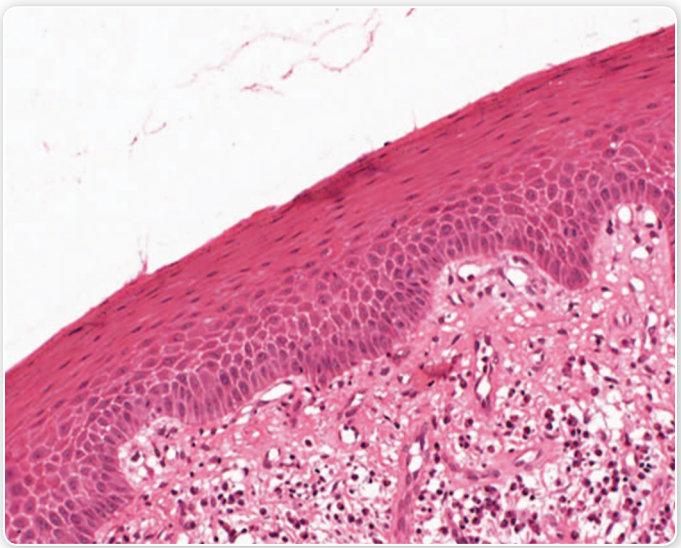


Squamous cell carcinoma of the buccal mucosa in a patient with oral submucous fibrosis.

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Chapter 6

Histopathology of Oral Precancers

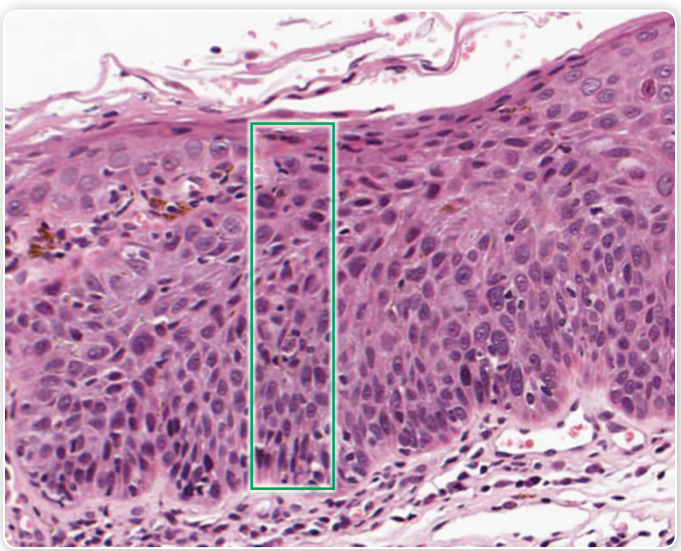


Normal parakeratinized stratified squamous epithelium.

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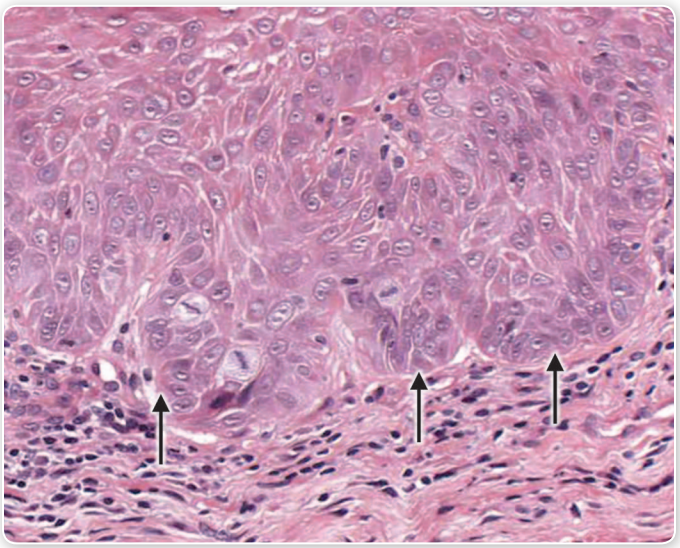
Features of dysplasia

Architecture
Irregular epithelial stratification
Loss of polarity of basal cells
Drop-shaped rete ridges
Increased number of mitoses
Premature keratinization in single cells (dyskeratosis)
Keratin pearls within rete pegs
Cytology
Abnormal variation in nuclear size (anisonucleosis)
Abnormal variation in nuclear shape (nuclear pleomorphism)
Abnormal variation in cell size (anisocytosis)
Abnormal variation in cell shape (cellular pleomorphism)
Increased nuclear-cytoplasmic ratio
Increased nuclear size
Atypical Mitotic figures
Increased number and size of nucleoli
Hyperchromasia

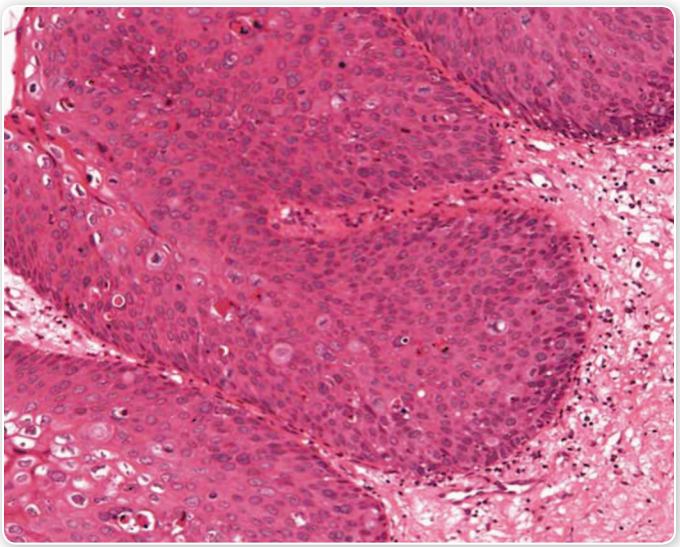


Irregular epithelial stratification (marked in green color).

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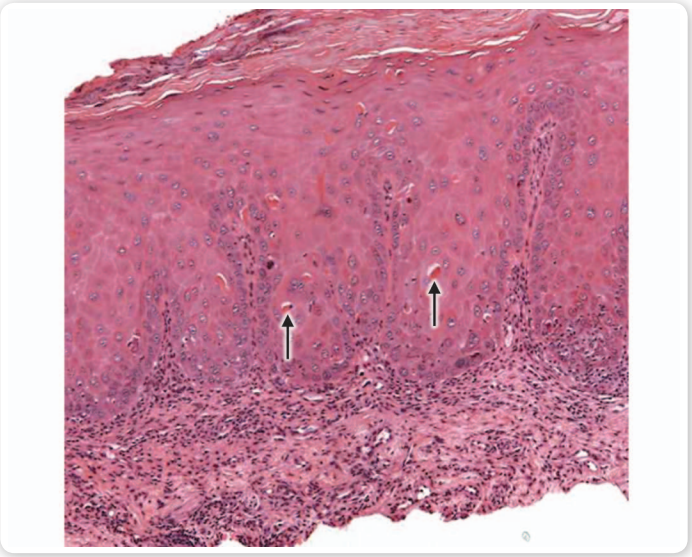


Loss of polarity of basal cells.

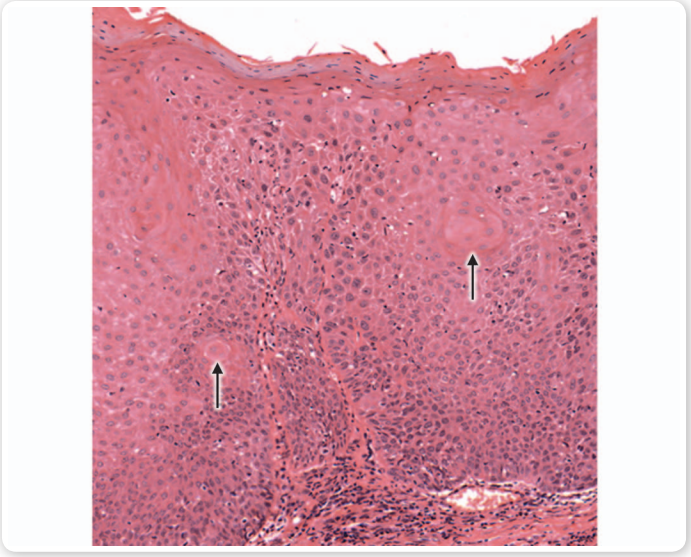


Drop-shaped rete ridges and increased mitosis.

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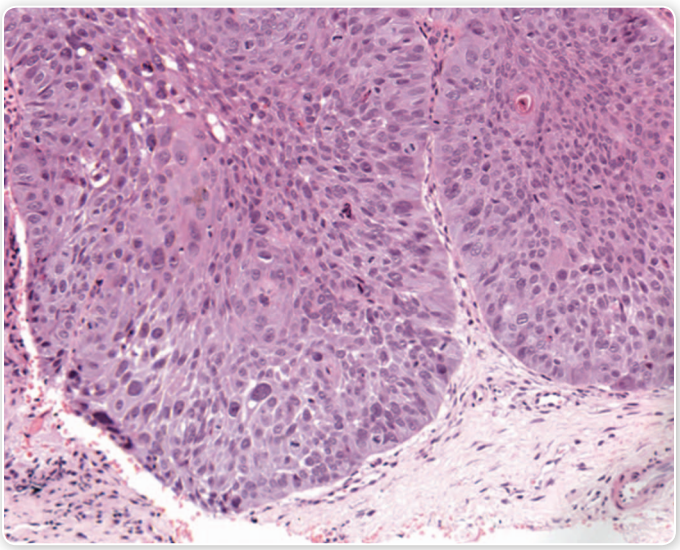


Premature individual cell keratinization.

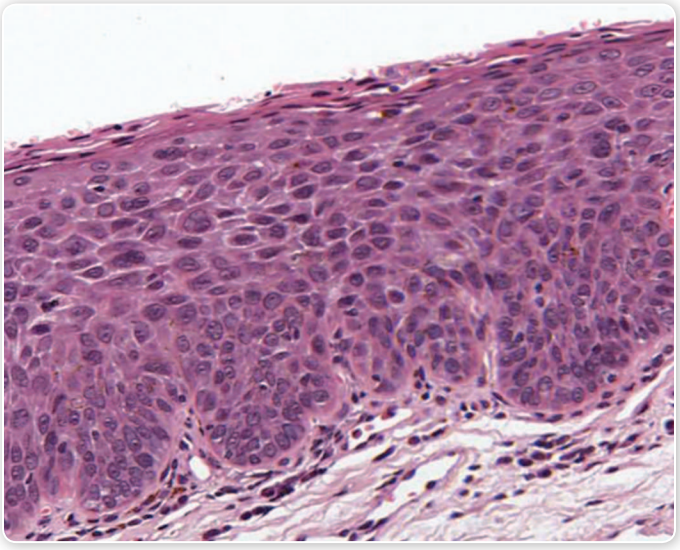


Keratin pearls within rete ridges.

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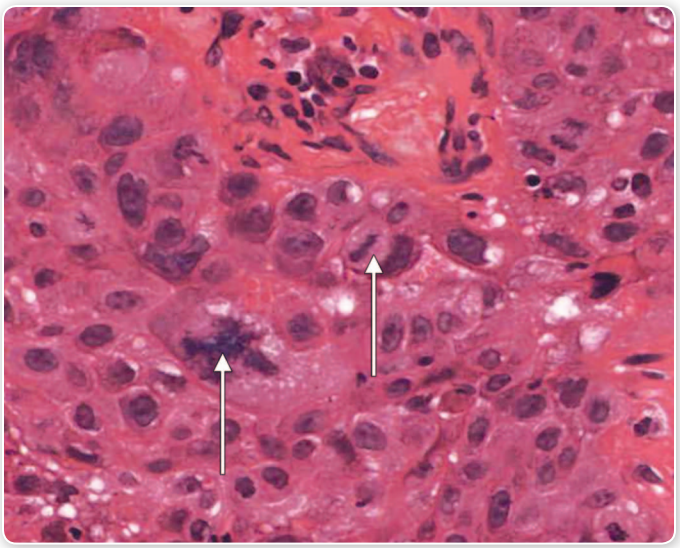


Abnormal variation in cell shape (cellular pleomorphism),
Abnormal variation in nuclear size (anisonucleosis),
Abnormal variation in nuclear shape (nuclear pleomorphism),
Abnormal variation in cell size (anisocytosis).

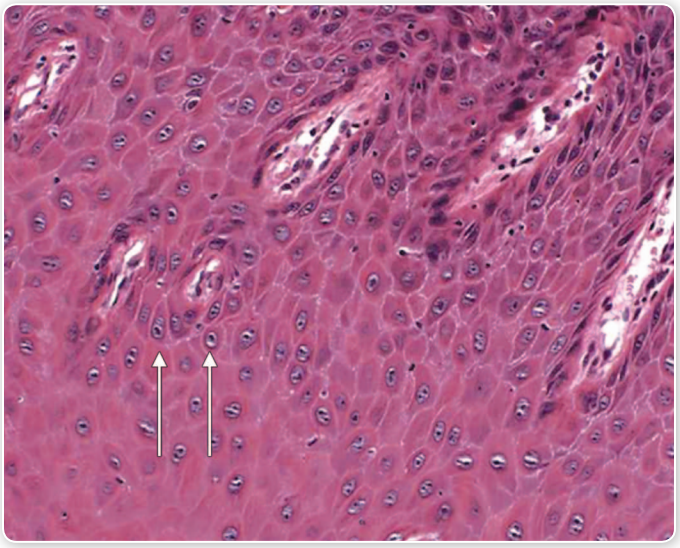


Increased nuclear cytoplasmic ratio, increased nuclear size
and cellular and nuclear pleomorphism.

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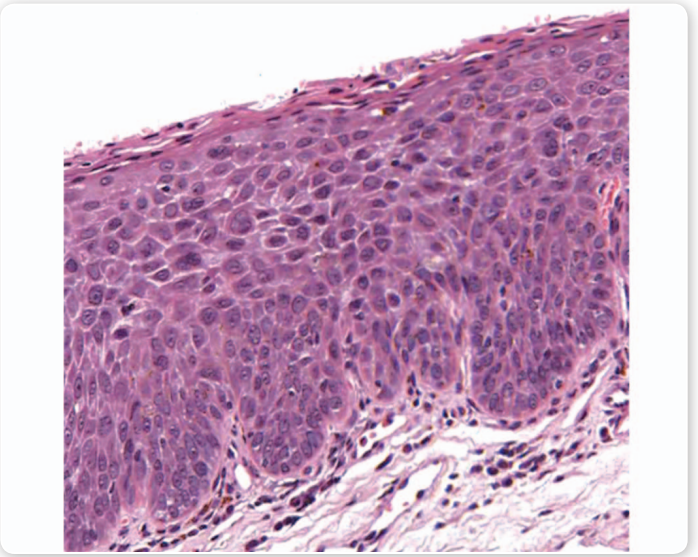


Abnormal mitosis.



Increased number of nucleoli.

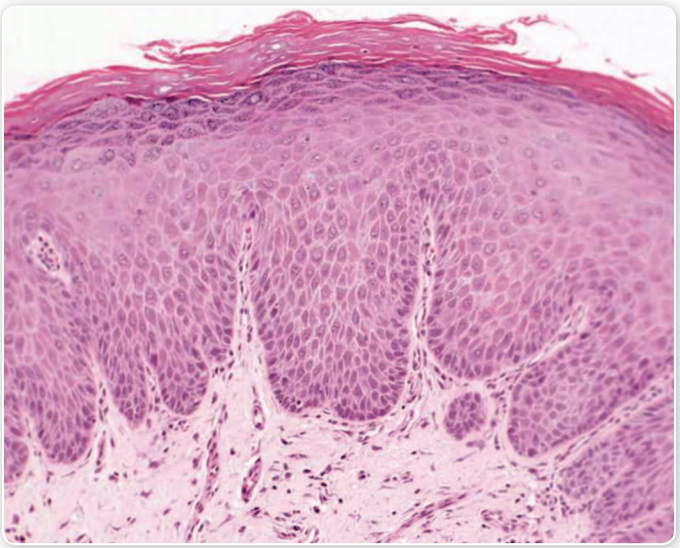
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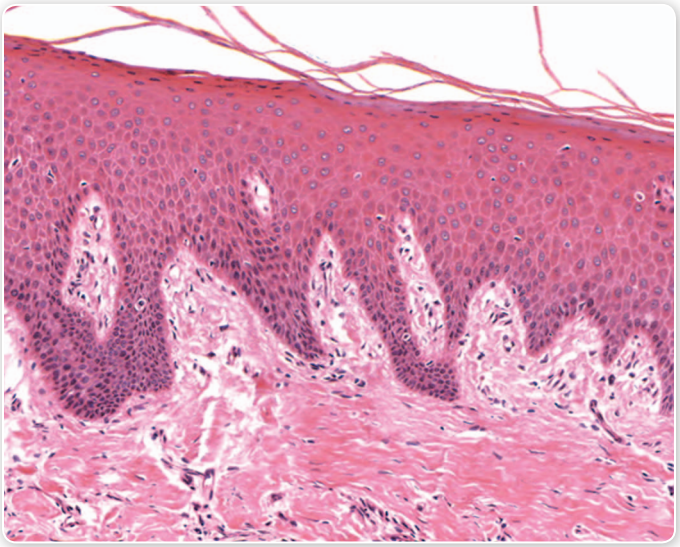
Hyperchromasia.

1	Squamous hyperplasia	This may be in the spinous layer (acanthosis) and/or in the basal/parabasal cell layers (basal cell hyperplasia); the architecture shows regular stratification without cellular atypia
2.	Mild dysplasia	The architectural disturbance is limited to the lower third of the epithelium accompanied by cytological atypia
3.	Moderate dysplasia	The architectural disturbance extends into the middle third of the eipthelium; consideration of the degree of cytological atypia may require upgrading
4.	Severe dysplasia	The architectural disturbance involves more than two–thirds of the epithelium: architectural disturbance into the middle third of the epithelium with sufficient cytologic atypia is upgraded from moderate to severe dysplasia
5.	Carcinoma in situ	Full thickness or almost full thickness architectural disturbance in the viable cell layers accompanied by pronounced cytological atypia

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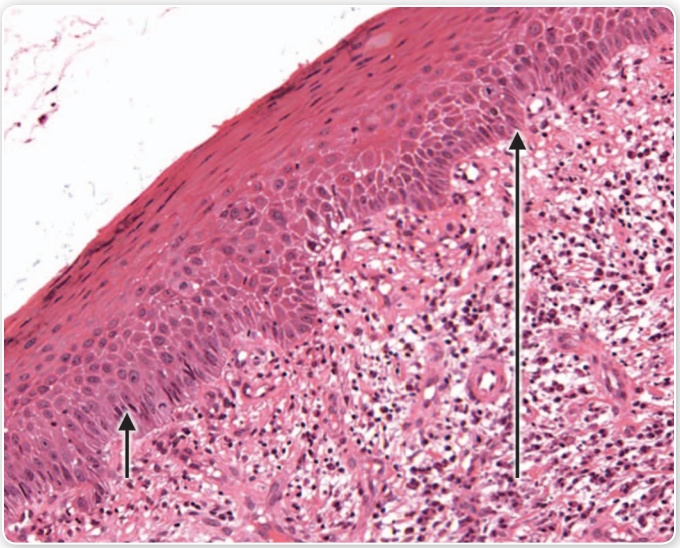


Squamous hyperplasia.

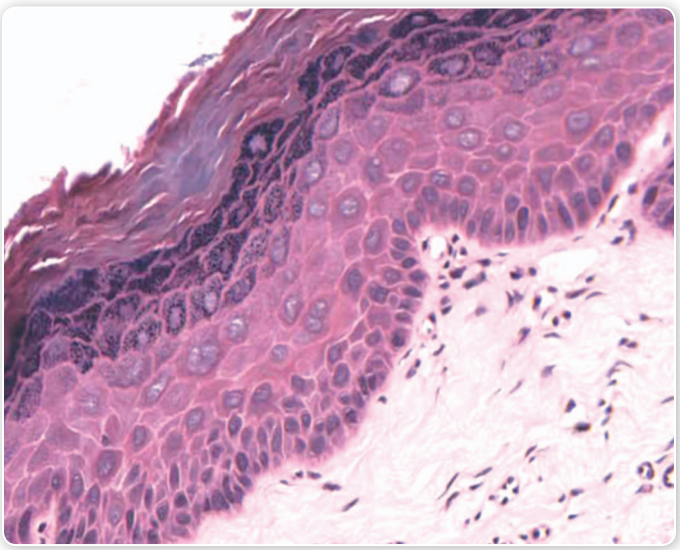


Squamous hyperplasia.

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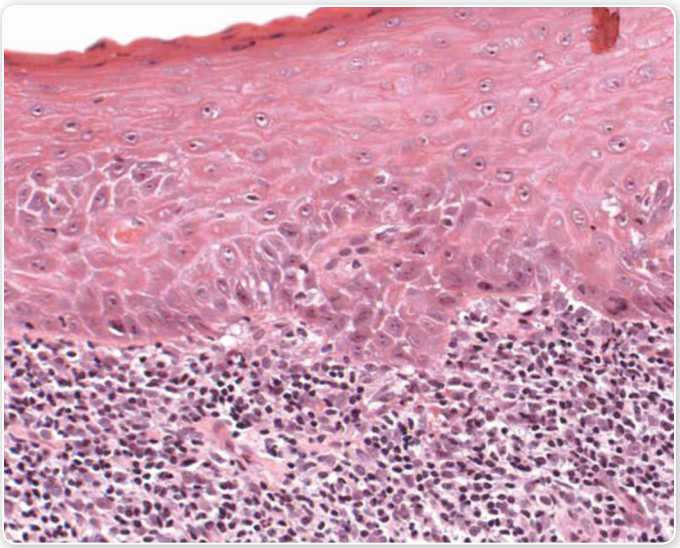


Portion of epithelium is mildly dysplastic and remaining part of epithelium is normal.

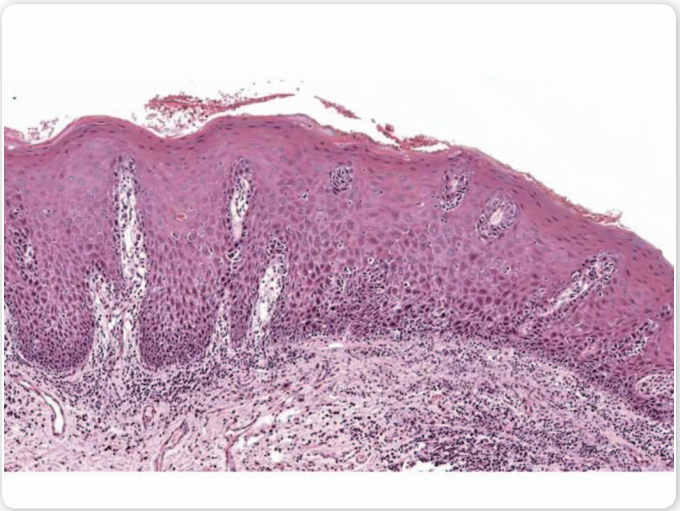


Mild dysplasia.

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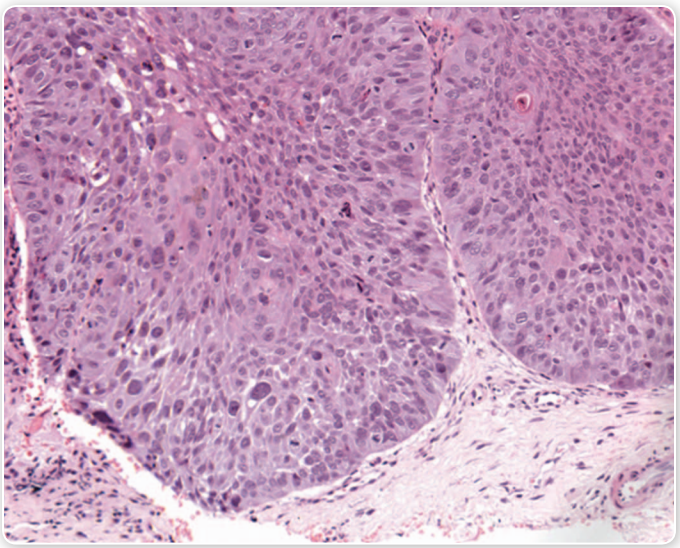


Mild dysplasia.

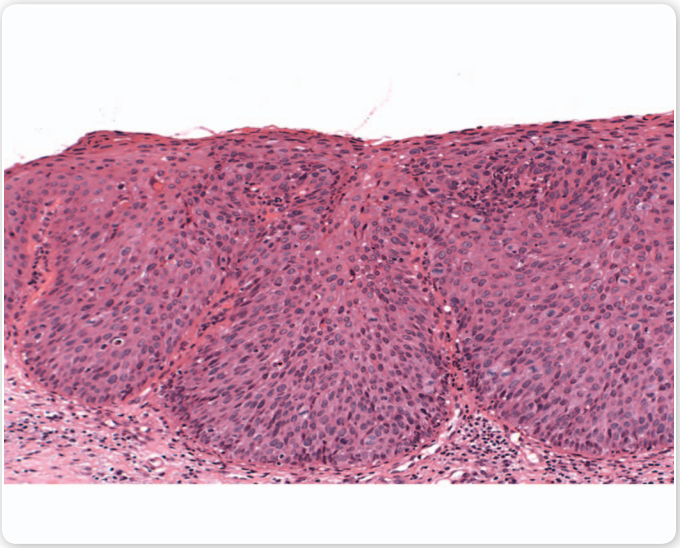


Moderate dysplasia.

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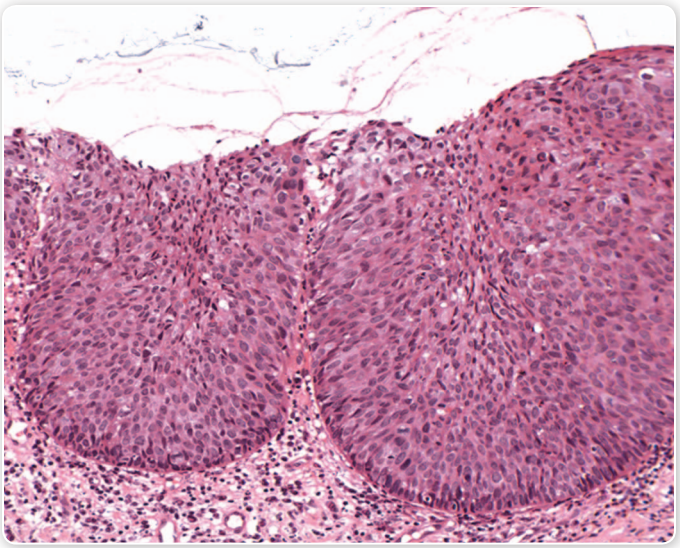


Severe dysplasia.



Severe dysplasia.

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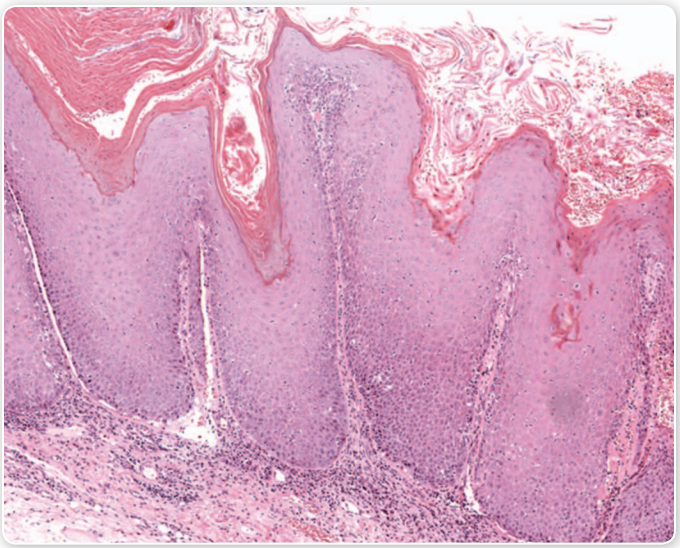


Carcinoma in situ.

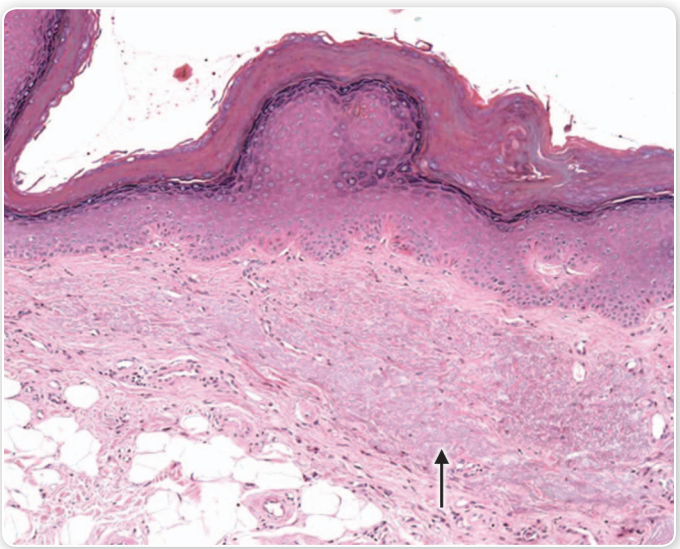


Hairy leukoplakia.

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Verrucous leukoplakia.



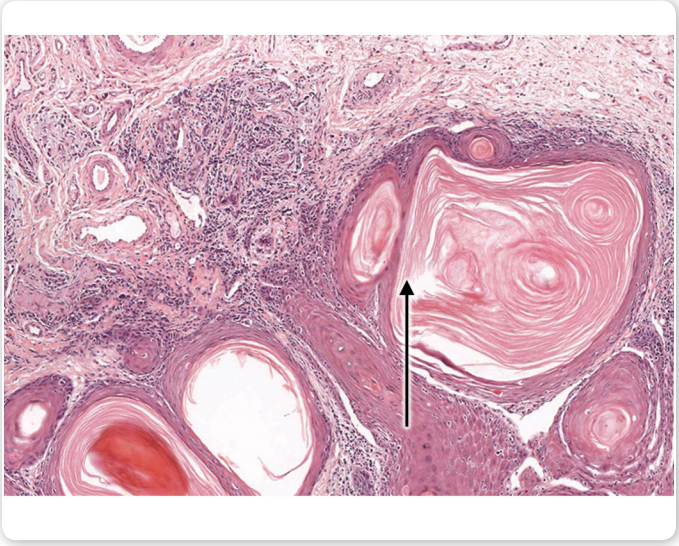
Actinic keratosis: Arrow showing actinic elastosis.

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Chapter 7

Histopathology of Squamous Cell Carcinoma

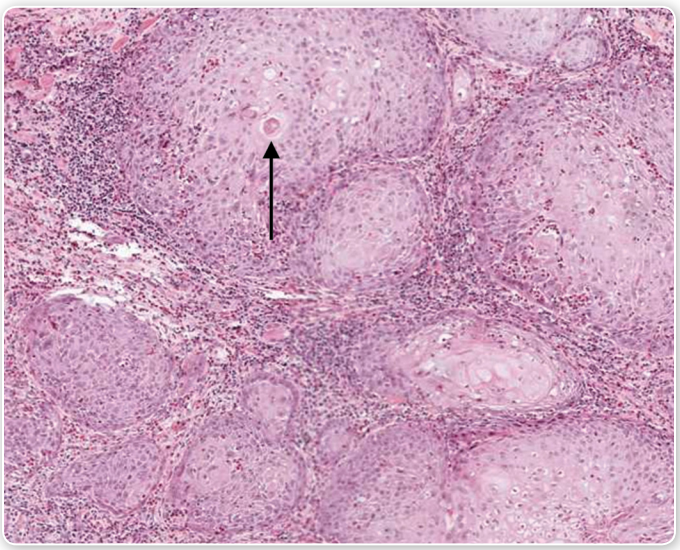
Well Differentiated SCC



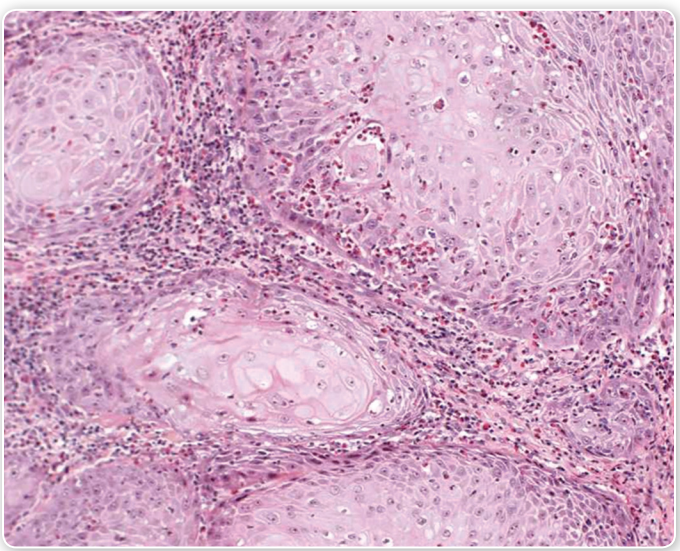
The islands of cells invading the connective tissue resemble stratified squamous epithelial cells. Arrow: Well-formed keratin pearls are seen in invading islands.

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Moderately Differentiated SCC



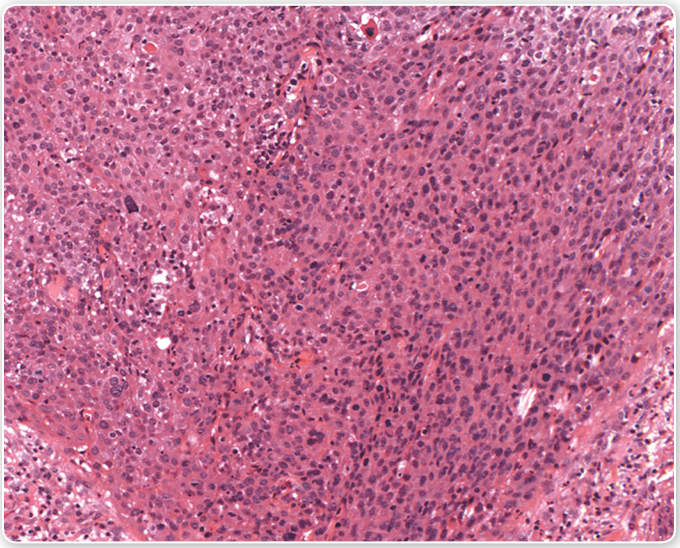
No well-formed keratin pearls seen. But the cells in the infiltrating islands are squamous epithelial cells and show individual cell keratinization (20X)



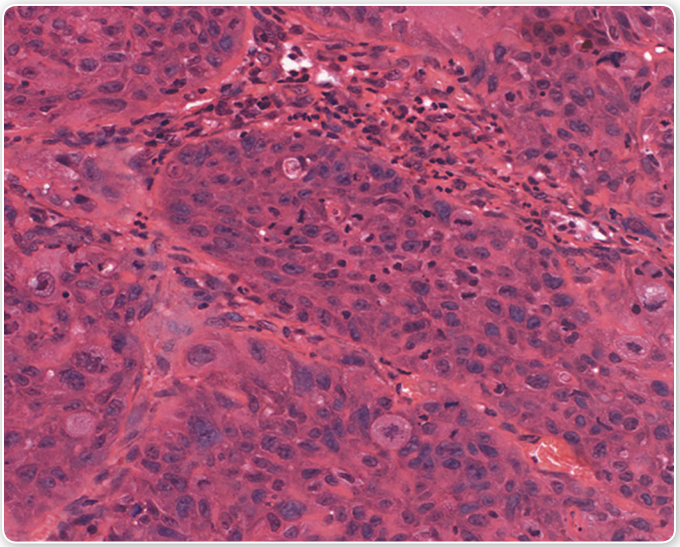
No well-formed keratin pearls seen. But the cells in the infiltrating islands are squamous epithelial cells and show individual cell keratinization (40X)

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Poorly Differentiated SCC

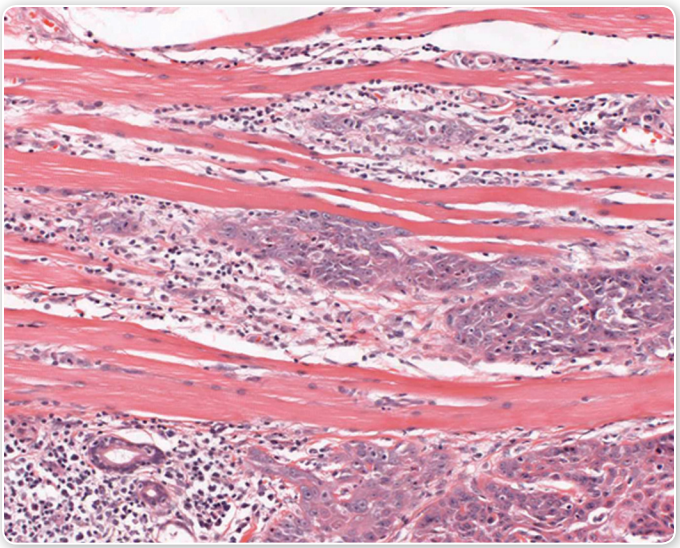


The malignant cells have minimum resemblance to cell of origin, i.e. squamous epithelial cell (20X).

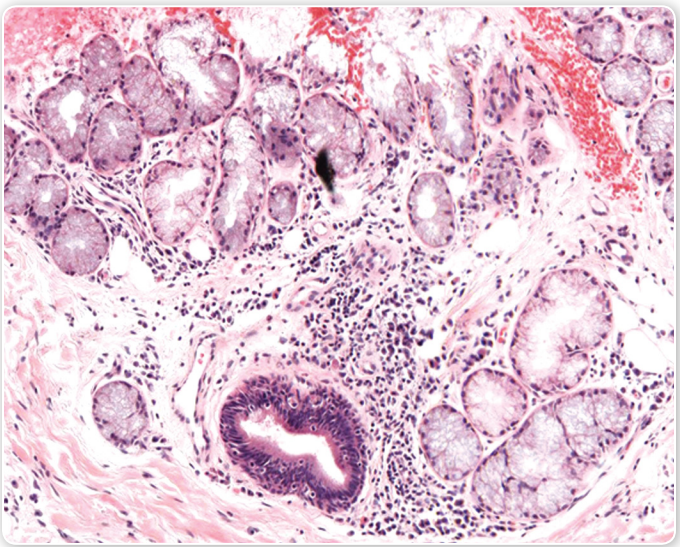


The malignant cells have minimum resemblance to cell of origin and numerous mitotic figures are seen.

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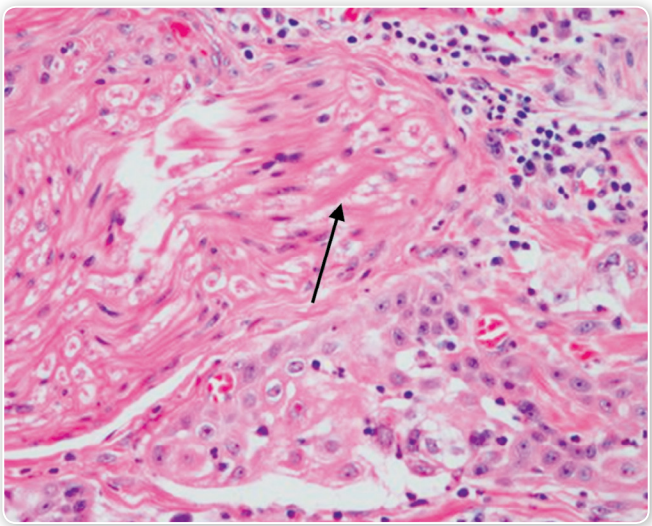
Malignant epithelial islands invading the muscle layer.



Dysplastic salivary gland duct in a poorly differentiated SCC.

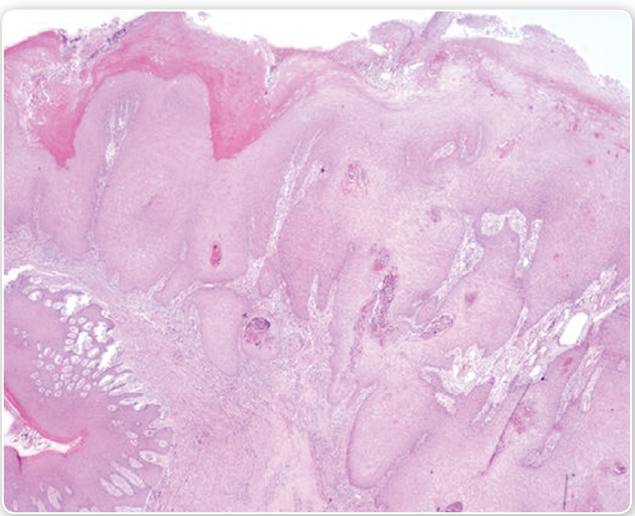
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Perineural Invasion



Nerve is surrounded by malignant squamous cells. Arrow shows-nerve tissue.

Source: Yanofsky VR, Mercer SE, Phelps RG. Histopathological variants of cutaneous squamous cell carcinoma: a review. J Skin Cancer. 2011.



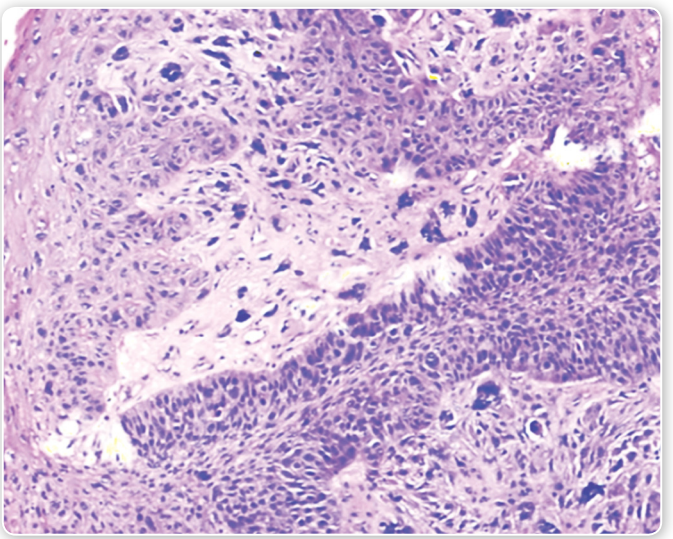
Broad, blunt, pushing, squamous epithelial downgrowths and without true invasion. Epithelium is well-differentiated, hyperkeratinized with minimum hyperchromatism and pleomorphism.

Source: Santoro A. et al. A troubling diagnosis of verrucous squamous cell carcinoma ("the Bad Kind" of Keratosis) and the need of clinical and pathological correlations: a review of the literature with a case report. J Skin Cancer. 2011.

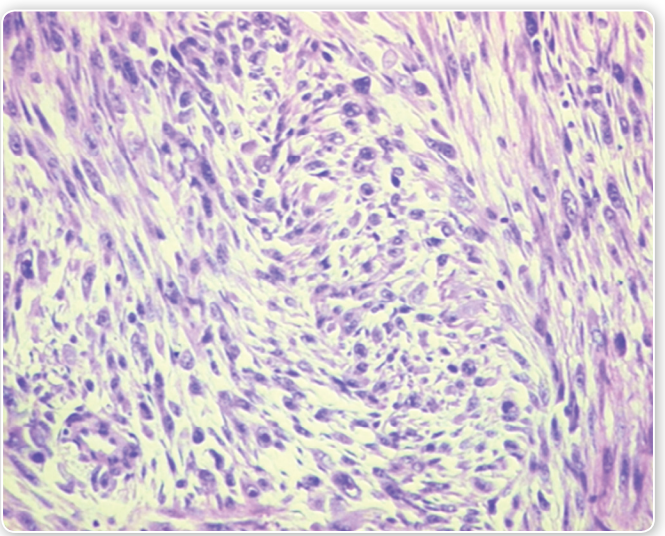
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OTHER RARE VARIANTS OF SCC

Spindle Cell Carcinoma



Nests of frank squamous carcinoma intimately admixed with spindle cell elements.

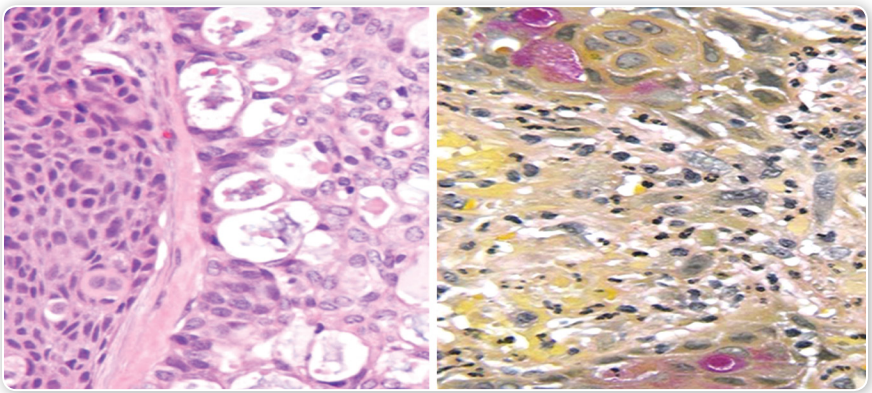


Spindle cells showing fasciculated arrangement of tumor cells.

Source: Viswanathan S, et al. Sarcomatoid (Spindle cell) carcinoma of the head and neck mucosal region: a clinicopathologic review of 103 cases from a tertiary referral cancer center. Head Neck Pathol. 2010;4(4): 265–75.

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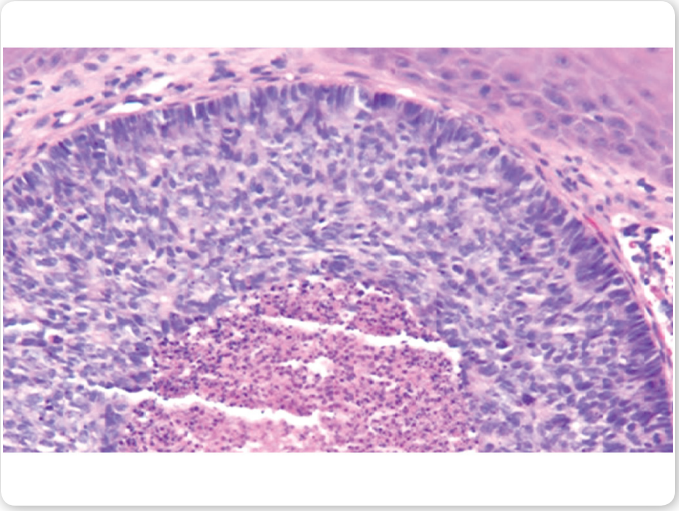
Adenosquamous Cell Carcinoma



Blend of adenocarcinoma and squamous cell carcinoma within a single tumor mass, adenomatous nature demonstrated by a mucicarmine stain.

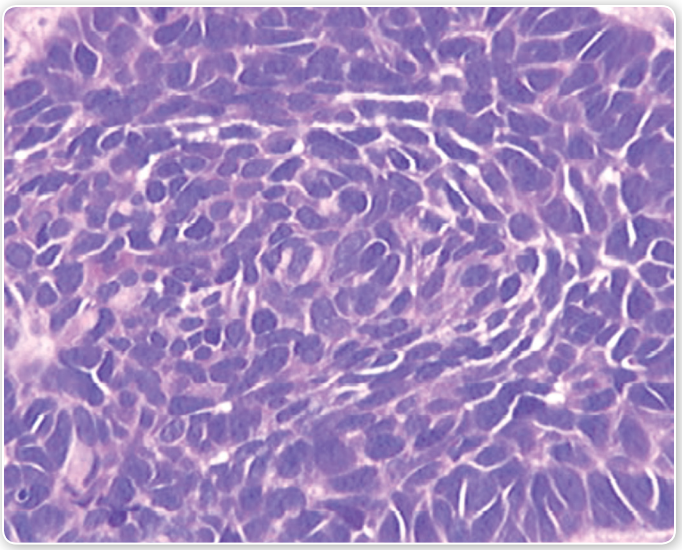
Source: Thompson L. Squamous cell carcinoma variants of the head and neck. Current Diagnostic Pathology. 2003;9:384–96.

Basaloid Squamous Cell Carcinoma



The basaloid component in close association with or involving the surface mucosa frequently demonstrates marked mitotic activity and comedonecrosis in the center of the neoplastic islands.

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The basaloid component seen as small, closely arranged, pleomorphic cells with hyperchromatic nuclei and scant cytoplasm in a lobular configuration.

Source: Thompson L. Squamous cell carcinoma variants of the head and neck. Current Diagnostic Pathology. 2003;9:384–96.

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Chapter 8

Metastasis

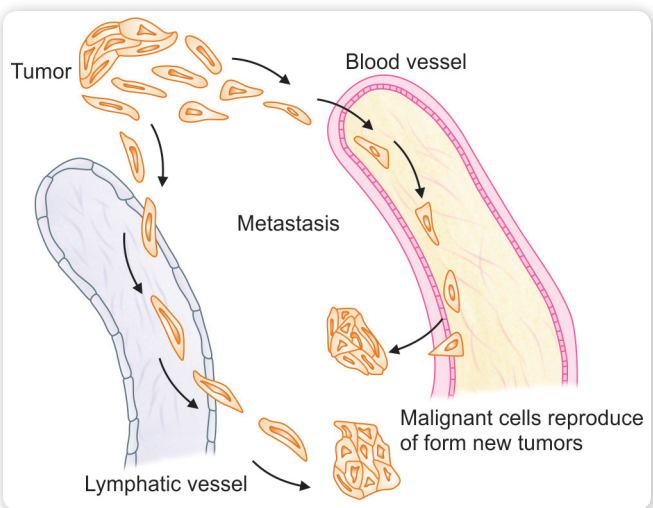
Routes of SCC spread:

a. By direct extension over mucosal surfaces, muscle and bone,
b. By dissemination via lymphatic drainage pathways,
c. By dissemination via blood vessels,
d. By extension along perineural space of nerve fibers (Perineural invasion is an uncommon route of spread in patients with SCC and is associated with a relatively poor prognosis) and
e. Transplantation or implantation (Mechanical carriage of fragments of tumor cells by surgical instruments during operation or the use of needles during diagnostic procedures).

Metastasis

The development of secondary malignant growths at a distance from the primary site.

Routes of Metastasis



Distant spread of the cancer cells from the primary is called metastasis.

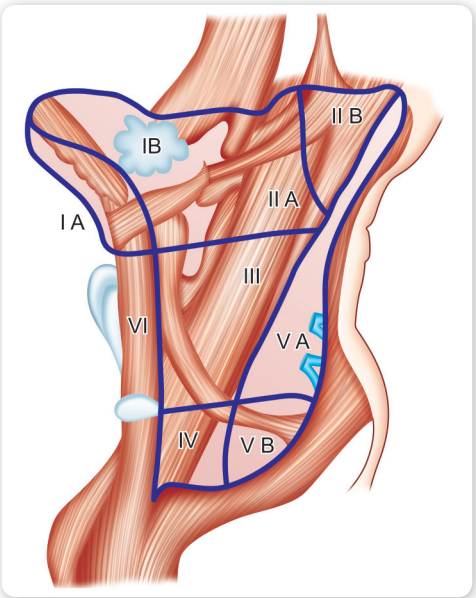
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TABLE 8.1: TNM classification of SCC of oral cavity and oropharynx

DISEASE CATEGORY	*DEFINING CHARACTERISTICS*
	PRIMARY TUMOR OF ORAL CAVITY
T x	Primary tumor cannot be assessed
T o	No evidence of primary tumor is seen
T is	Primary tumor is carcinoma in situ
T 1	Primary tumor has a maximum diameter of 2 cm or less
T 2	Primary tumor has a maximum diameter of more than 2 cm but no more than 4 cm
T 3	Primary tumor has a maximum diameter of more than 4 cm
T 4a Lip Oral cavity	Primary tumor involves cortical bone, inferior alveolar bone, floor of the mouth, skin Primary tumor involves cortical bone, intrinsic and extrinsic muscles of tongue, maxillary sinus and skin
T 4b	Primary tumor involves maxillary space, pterygoid plates, skull base and internal carotid artery
	PRIMARY TUMOR OF OROPHARYNX
T x	Primary tumor cannot be assessed
T o	No evidence of primary tumor is seen
T 1	Primary tumor has a maximum diameter of less than 2 cm
T 2	Primary tumor has a maximum diameter of 2–4 cm
T 3	Primary tumor has a maximum diameter of more than 4 cm
T 4a	Primary tumor involves Primary tumor involves larynx, intrinsic and extrinsic muscles of tongue, median pterygoid muscle, hard palate, mandible
T 4b	Primary tumor involves lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, skull base, carotid artery
	REGIONAL METASTASIS
N X	Regional lymph nodes cannot be assessed
N O	No regional lymph node metastasis is evident
N 1	Ipsilateral single enlarged lymph node with a maximum diameter of less than 3 cm
N 2a	Ipsilateral single enlarged lymph node with a maximum diameter of 3-6 cm
N 2b	Ipsilateral single enlarged lymph node with a maximum diameter of less than 6 cm
N 2c	Bilateral or contralateral enlarged lymph nodes with a maximum diameter of less than 6 cm
N 3	Enlarged node with a maximum diameter of more than 6 cm
	DISTANT METASTASIS
M X	Distant metastasis not assessed
M O	No distant metastasis is evident
M 1	Distant metastasis is evident

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Cancer stage	*T CATEGORY*	*N CATEGORY*	*M CATEGORY*
0	Tis	N 0	M 0
I	T 1	N 0	M 0
II	T 2	N 0	M 0
III	T 1, T 2 T 3	N I N 0, N 1	M 0 M 0
IV A	T 1, T 2, T 3 T 4a	N 2 N 0, N 1, N 2	M 0 M 0
IV B	Any T 4b	N 3 Any	M 0 M O
IV C	Any	Any	M1

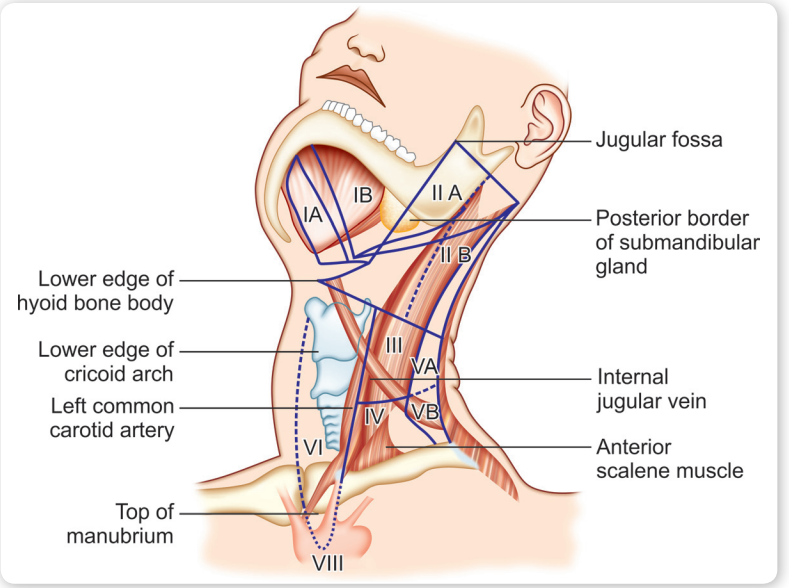


Groups of lymph node and associated structures in resected specimen

Groups of lymph nodes in each level:

- Level I: Submental and submandibular nodes
 - Level Ia: Submental triangle
 - Level Ib: Submandibular triangle
- Level II: Upper jugular nodes
- Level III: Middle jugular nodes
- Level IV: Lower jugular nodes
- Level V: Posterior triangle group
- Level VI: Anterior triangle group
- Level VII: Upper mediastinal nodes

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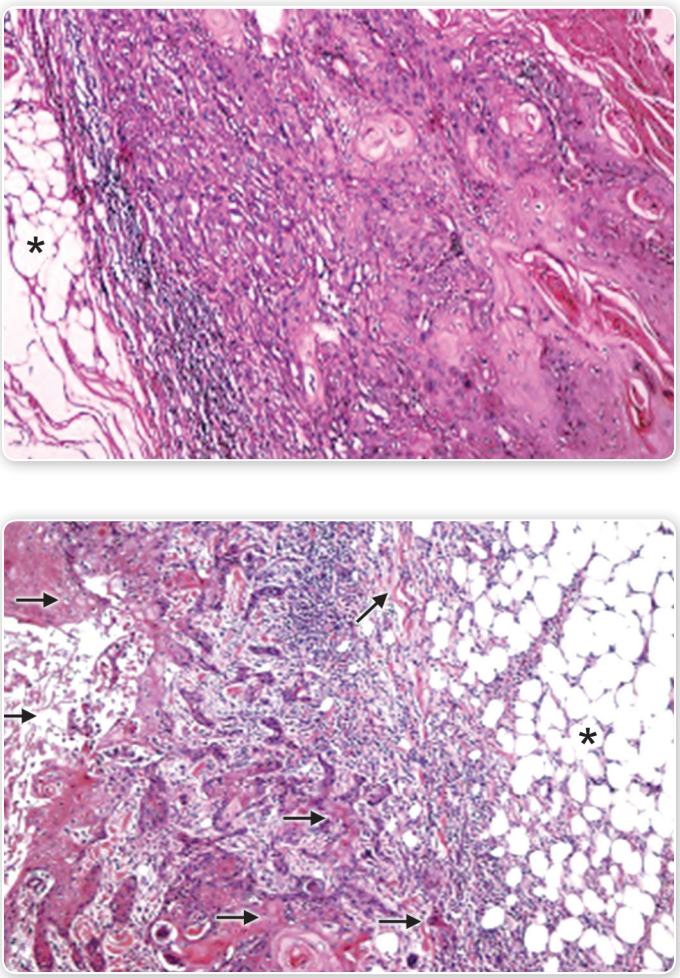


Groups of lymph nodes and associated structures

- Region I: Submental and submandibular triangles.
 - Ia: is the submental triangle bound by the anterior bellies of the digastric and the mylohyoid.
 - Ib: is the triangle formed by the anterior and posterior bellies of the digastric and body of mandible.
- Region II: Upper third including the upper jugular and jugulo digastric nodes and the upper posterior cervical nodes. Region bound by the digastric muscle superiorly and the hyoid bone (clinical landmark), or the carotid bifurcation (surgical landmark) inferiorly.
 - IIa: contains nodes in the region anterior to the spinal accessory nerve.
 - IIb: postero-superior to the nerve.
- Region III: Middle third jugular nodes extending from the carotid bifurcation superiorly to the cricothyroid notch (clinical landmark), or inferior edge of cricoid cartilage (radiological landmark), or omohyoid muscle (surgical landmark).
- Region IV: Lower jugular nodes extending from the omohyoid muscle superiorly to the clavicle inferiorly.
- Region V: Posterior triangle group of lymph nodes located along the lower half of the spinal accessory nerve and the transverse cervical artery. The supraclavicular nodes are also included in this group. The posterior boundary is the anterior border of the trapezius muscle, the anterior boundary is the posterior border of the sternocleidomastoid muscle, and the inferior boundary is the clavicle.
- Region VI: Anterior compartment group comprises lymph nodes surrounding the midline visceral structures of the neck extending from the level of the hyoid

bone superiorly to the suprasternal notch inferiorly. On each side, the lateral boundary is the medial border of the carotid sheath. Located within this compartment are the perithyroidal lymph nodes, paratracheal lymph nodes, lymph nodes along the recurrent laryngeal nerves, and precricoid lymph nodes.

- Level VII: To denote lymph node groups in the superiormediastinum is no longer used.



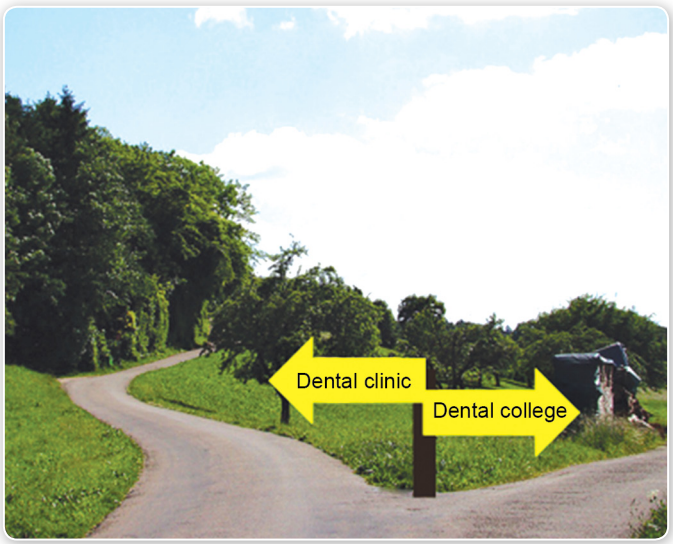
Squamous cell carcinoma in the lymph node.

Source: Greenberg JS, et al. Extent of extracapsular spread. A critical prognosticator in oral tongue cancer. Cancer. 2003;97:1464-70.

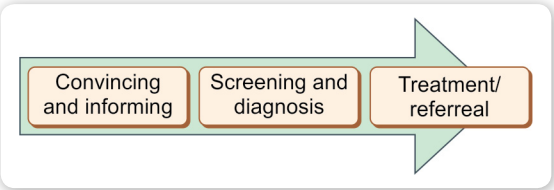
Chapter 9

Screening for Oral Cancers and Potentially Malignant Disorders

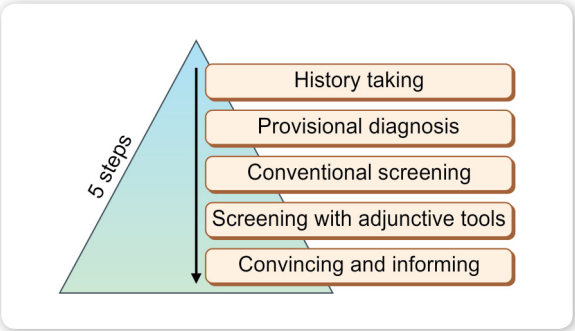
Screening can be done at Dental clinic or at Dental colleges



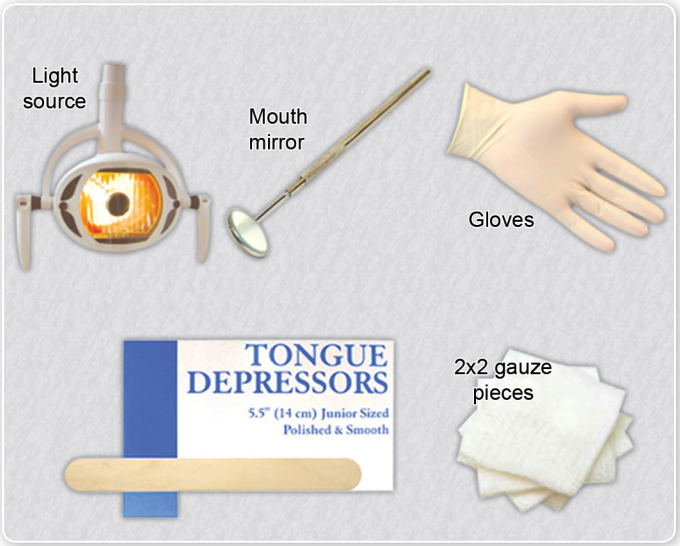
Steps to be followed for early diagnosis and treatment



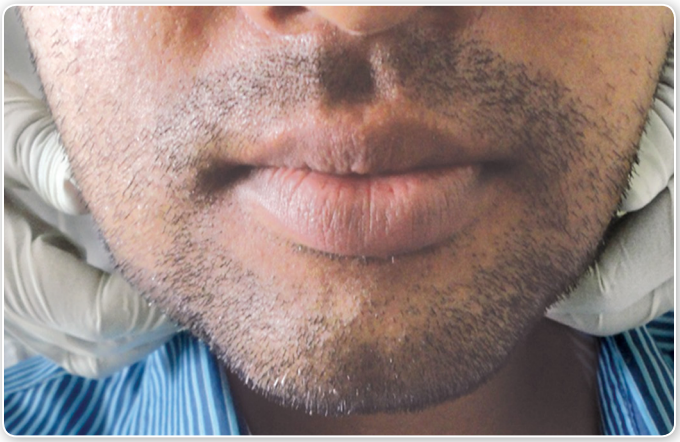
Steps to be followed for early diagnosis



Materials required for conventional screening



Extra Oral Examination of Lymph Nodes



Submandibular lymph node examination.



Palpation of the anterior cervical nodes.



Palpation of the posterior cervical nodes.



Bilateral palpation of the supraclavicular lymph nodes.



Preauricular nodes.



Postauricular nodes.

Intraoral Examination





Evert the lips and visually examine the labial mucosa and sulcus of the maxillary vestibule and the mandibular vestibule along with the frenum.



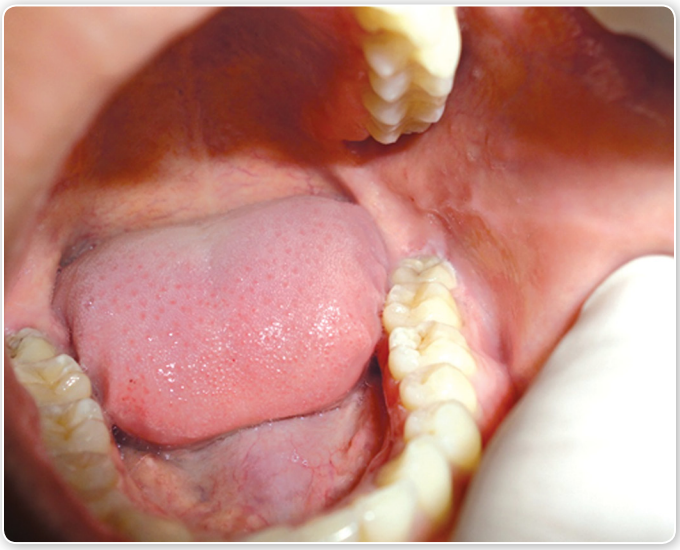
Bidigital palpation of the tissues of the lips.



Retract the buccal mucosa with the mouth mirror.



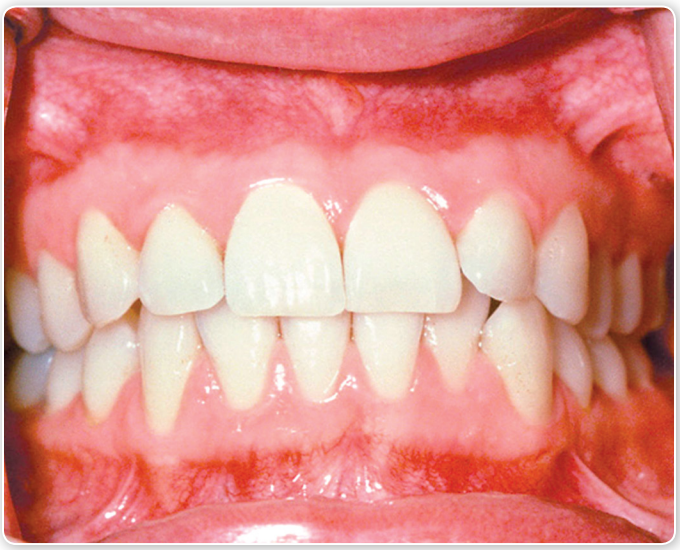
Examine the buccal mucosa extending from the labial commissure and back to the anterior tonsillar pillar.



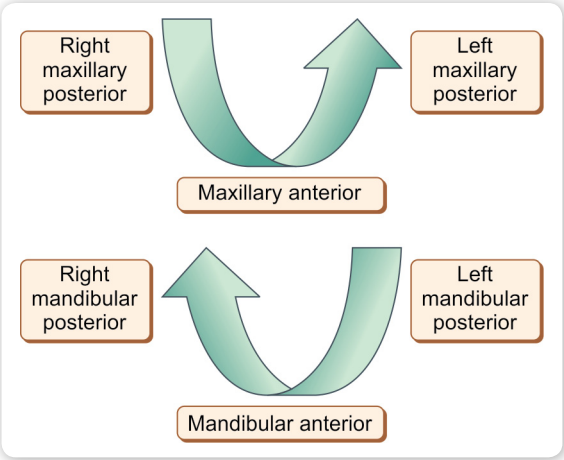
Pull the tissues away from the retromolar area and screen retromolar area.



The buccal mucosa should be bidigitally palpated pressing the tissue between the index finger and thumb of one hand.



Examine the buccal and labial aspects of the gingiva followed by examination of the palatal and lingual aspects.



Order of examination of dental arch.



Examine dorsum of the tongue by instructing the patient to put the tongue out.



The lateral borders of the tongue are examined by grasping the tip of the tongue with a gauze sponge, extending and rotating it laterally.



Use the mirror to examine the posterior lateral borders, if necessary.



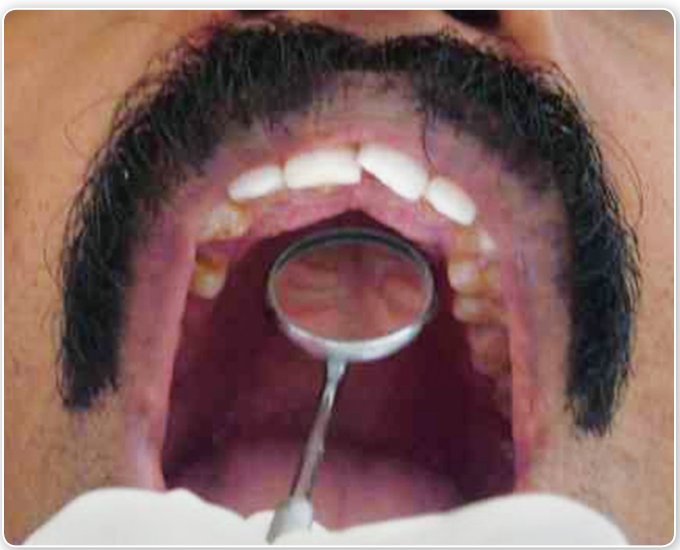
The ventral surface of the tongue is most easily visualized by having the person touch the roof of the mouth with tip of the tongue.



With the tongue still elevated, inspect the floor of the mouth for changes in color, texture, swellings, or other surface abnormalities.



Use a bidigital technique to palpate the entire tongue between the finger and thumb of one hand.

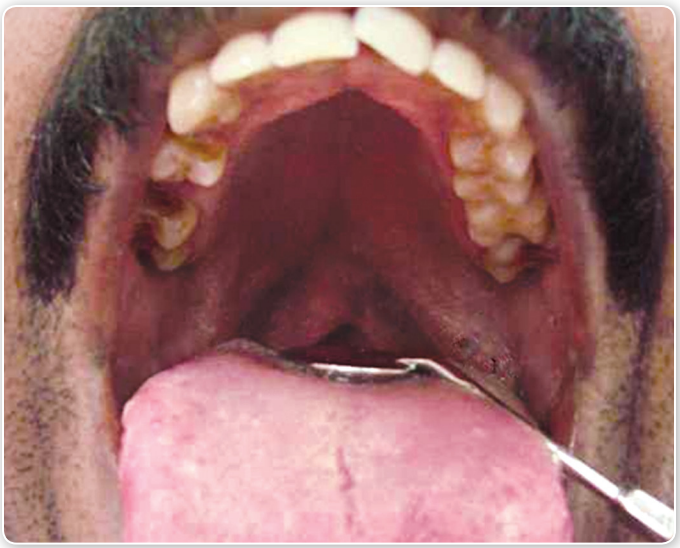




The hard palate and maxillary tuberosity areas are re-examined using both direct and indirect vision.



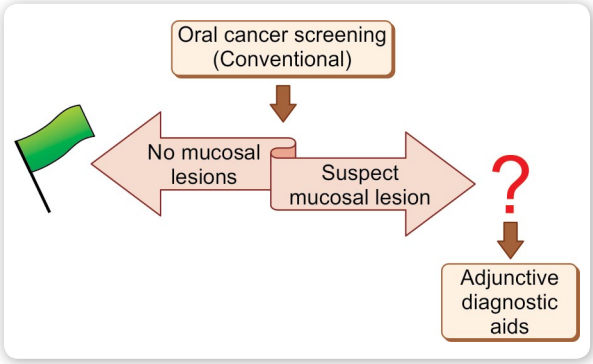
Following the visual examination the clinician should digitally palpate the entire area using firm nonsliding pressure against the bone.



The soft palate is examined by depressing the base of the tongue with a tongue depressor and asking the subject to say “aah”.

Chapter 10

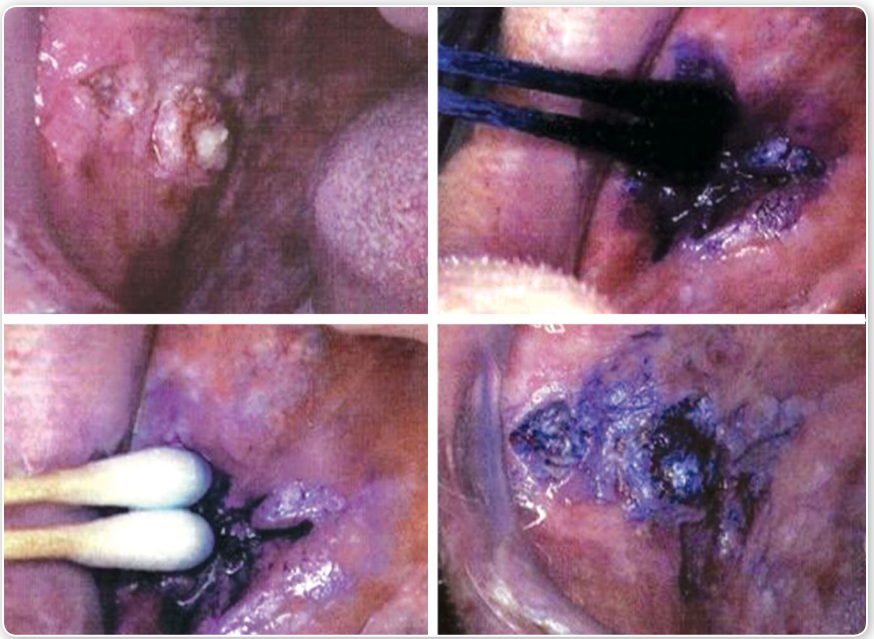
Diagnosis

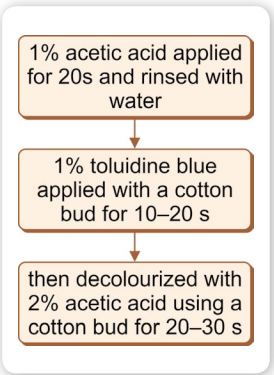


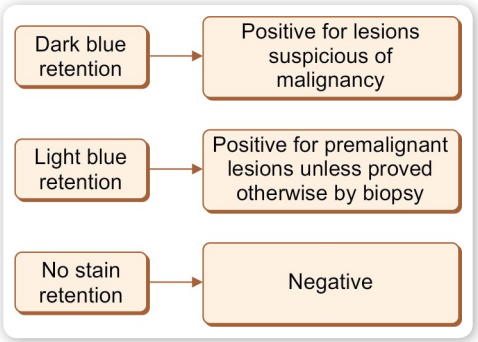
VISUAL EXAMINATION WITH VITAL TISSUE STAINING

Toluidine blue staining



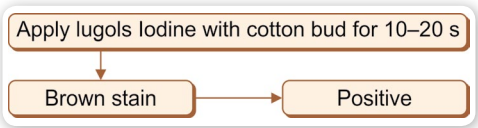






TB is a basic metachromatic nuclear stain which stains nuclear material of malignant lesions and PML.

LUGOL'S IODINE



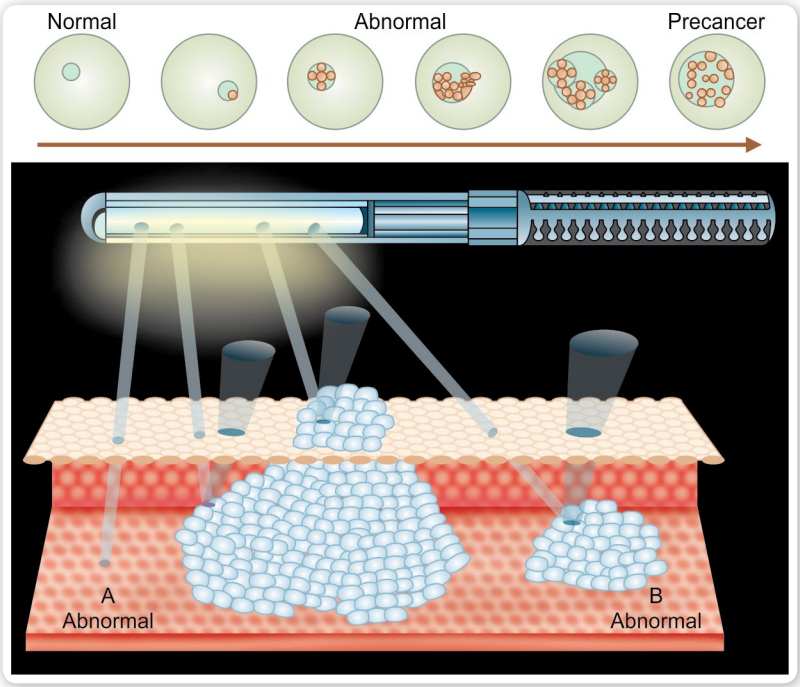
VISUALIZATION ADJUNCTS

ViziLite and ViziLite Plus with T Blue from Zila Pharmaceuticals, Phoenix, and MicroLux DL from AdDent Inc., Danbury, Connecticut.

Adjunct based on tissue reflectance

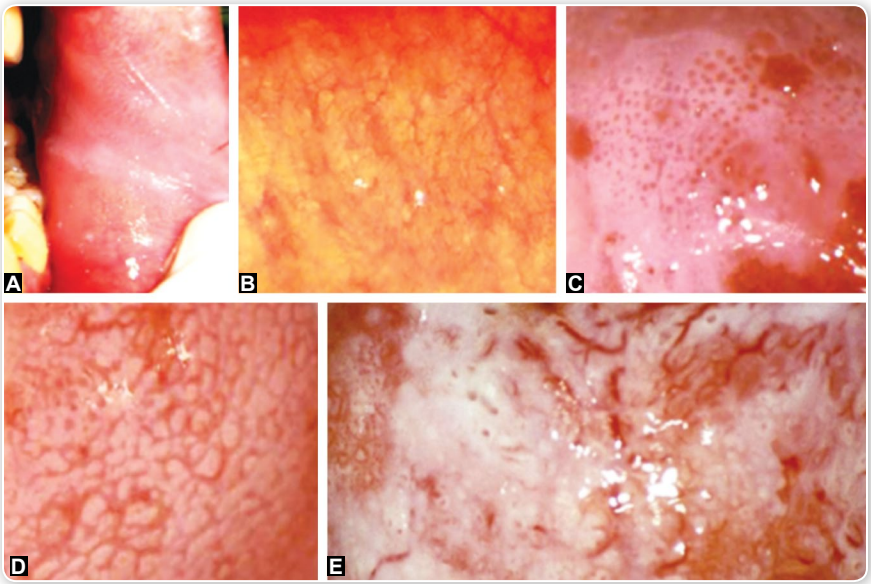


A brown bottle of 1% acetic acid solution and the disposable chemiluminescence light source package.



Principle: It is based upon the assumption that abnormal metabolic or structural changes have different absorbance and reflectance properties.

Colposcopy (direct intraoral microscopy)



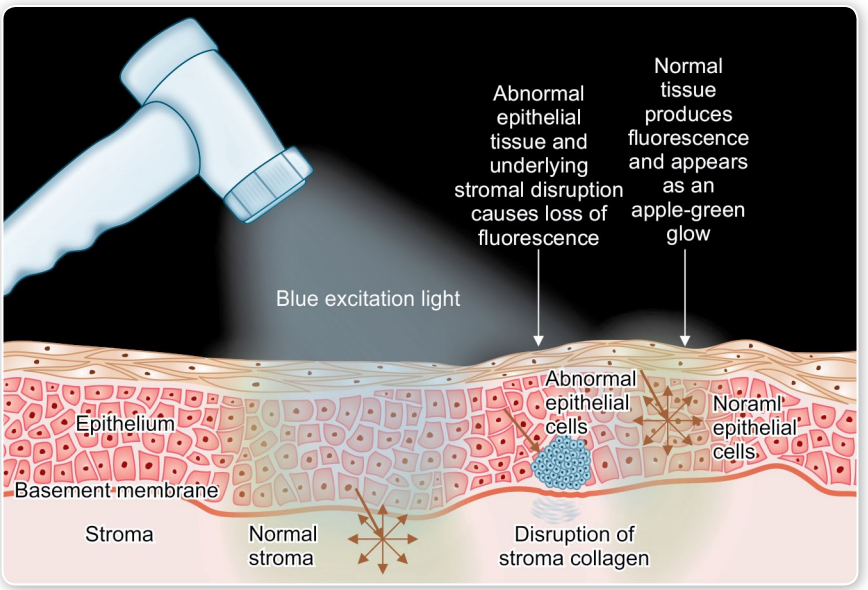
A. Hairpin capillary pattern in normal buccal mucosa.
B. Network capillary pattern in normal buccal mucosa.
C. Punctation vessel pattern in buccal mucosa carcinoma.
D. Mosaic pattern in buccal mucosa carcinoma.
E. Atypical vessel pattern in buccal mucosa carcinoma.

Principle: Colposcopic criteria include vascular pattern, inter-capillary distance, surface pattern, color tone and opacity, as well as clarity of demarcation of the mucosal lesions.

Source: Nayyar AS, Khan M, Gayitri HC, Bafna UD, Ahmed S. Review on clinical implications of colposcopy in oral squamous cell carcinoma: a practical approach. Middle East J of Cancer 2013; 4(2): 63-7.

Adjunct based on tissue autofluorescence





VELscope

Source: www.kenbeadlingdentistry.com.

Principle: Fluorophores within the tissue exposed to UV or visible light, can re-emit some of this light at longer wavelength in the form of fluorescence. Loss of autofluorescence due to a decrease in fluorescent crosslinks associated with stromal changes that underlies the neoplastic lesion.

Identafi 3000



Source: surgicalsolutionsusa.com/specialTrimera.pd



Carcinoma



Severe dysplasia

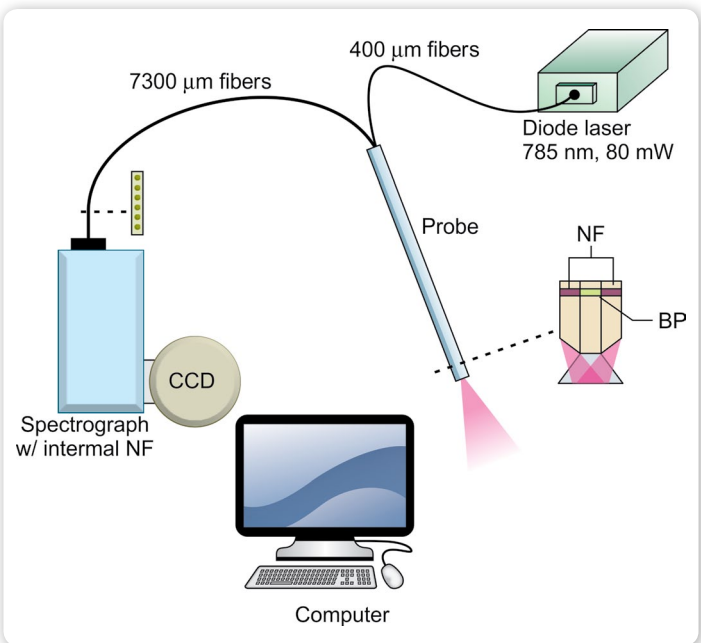
a. Lesion on the ventral surface of the tongue seen with the white reflectance (regular light) of Identafi 3000 DentalEZ optical device.
b. Green amber reflectance light show increase vascularity in the suspicious areas.
c. Violet fluorescent light shows dark area (loss of autofluorescence) in suspicious areas.

Principle: The combined system uses properties of fluorescence and reflectance of the tissue. Conventional examination of tissue is performed using white light. Violet light enhances normal tissue's natural fluorescence, and suspicious tissue appears dark because of its loss of fluorescence. Amber light, enhances normal tissue's reflectance properties. The abnormal tissue vasculature indicated by loss of reflectance.

Source: Lane P, Follen M, MacAulay C. Has fluorescence spectroscopy come of age? A case series of oral precancers and cancers using white light, fluorescent light at 405 nm, and reflected light at 545 nm using the trimira Identafi 3000. Gender Medicine/2012;9 (suppl 1):578-82.

Spectroscopy

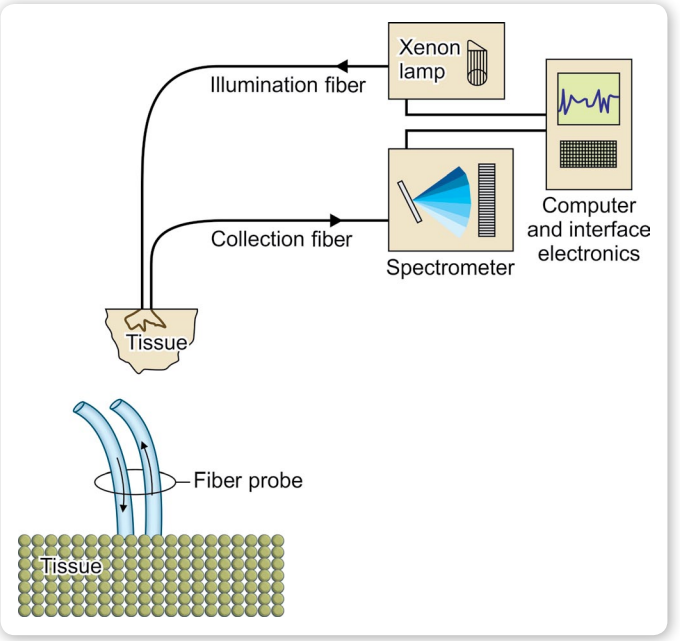
Surface enhanced Raman spectroscopy (SERS)



Source: Vargis E, Jansen AM. Using Raman spectroscopy to detect malignant changes in tissues. Department of Biomedical Engineering. Vanderbilt University.

Principle: SERS is a laser based technique which helps in the chemical characterization and to detect structure of molecules in the sample. A photon excites the molecule from the ground state to a virtual energy state. When that molecule relaxes, it emits a photon and it returns to a different rotational or vibrational state. The difference in energy between the original state and this new state leads to a shift in the emitted photon's frequency away from the excitation wavelength.

Elastic scattering spectroscopy



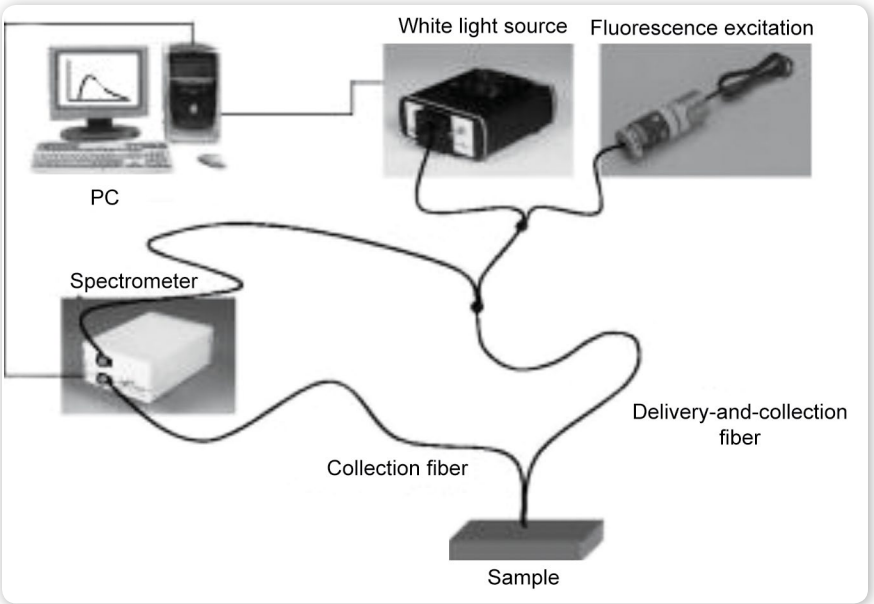
Schematic diagram of elastic scattering spectroscopy system.

Source: Sharwani A, et al. Assessment of oral premalignancy using elastic scattering spectroscopy. Oral Oncol. 2006;42:343–9.

Principle: The principle behind this technique is generation of wavelength dependent spectrum that reflects structural and morphological changes within the tissue. The structures that induces the scattering are the nucleus, chromatin concentration and cellular organelles.

The system uses a light of wide band of wavelengths from 400 nm up to 700 nm.

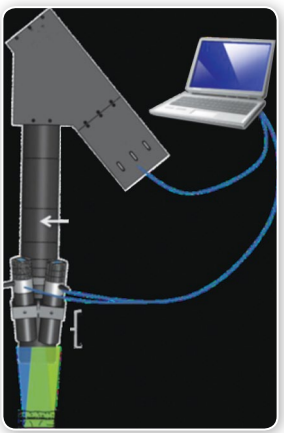
Differential path length spectroscopy

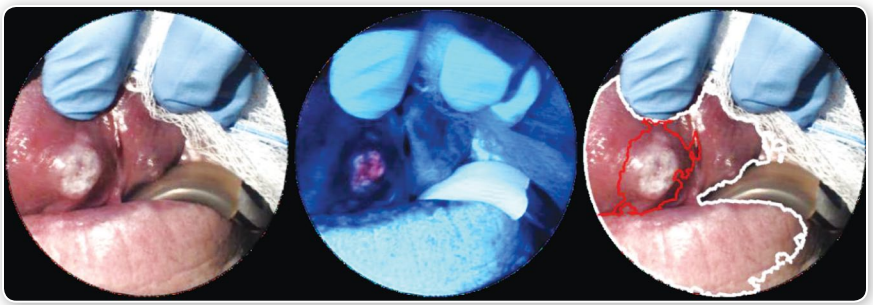


Source: Amelink A, et al. Quantitative fluorescence spectroscopy in turbid media using fluorescence differential path length spectroscopy. J Biomedopt.2008;13(5):54051.

Principle: It is a fiberoptic point measurement technique. It measures the scattered photons that have travelled, and their predetermined path lengths. The spectrum is analyzed mathematically and is translated into a set of parameters that are related to the microvasculature and to the intracellular morphology.

Multimodal snapshot imaging spectrometer



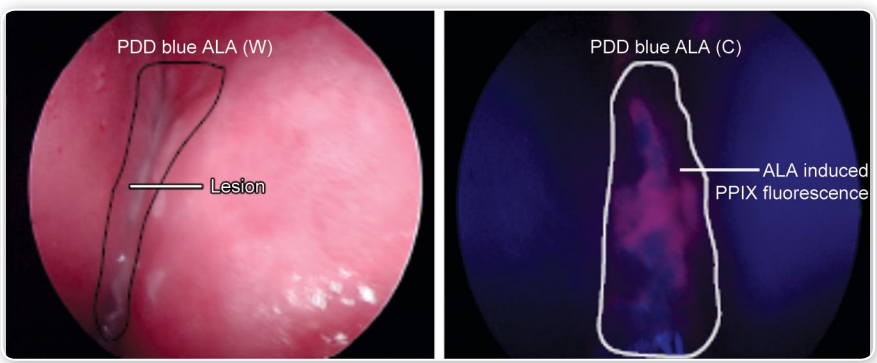


Spectral imaging from invasive carcinoma patient. The lesion in white light. Loss of autofluorescence in the lesion but boundaries are not clear. Spectral analysis done to determine the tissue region (white line) with areas of reduced autofluorescence highlighted (red line).

Principle: Autofluorescence emission (i.e. collagen, NADH, FAD) and reflectance features (i.e. oxy- and deoxy-hemoglobin). Light used is in the wavelength range of 471–667 nm obtained by a bandpass filter placed behind the camera lens.

Source: Bedard N, et al. Multimodal snapshot spectral imaging for oral cancer diagnostics: a pilot study. Biomedi opt Express. 2013;4(6):938-49.

Fluorescence endoscopy using 5-ALA (5-Aminolevulinic acid)

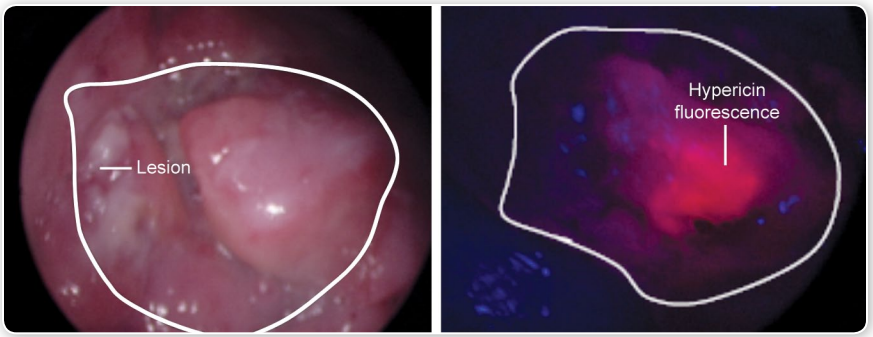


Images of white light (left) and ALA induced PPIX fluorescence (right) of an oral lesion obtained using a fluorescence endoscopy system.

Principle: 5-aminolevulinic acid (5-ALA) is a photosensitizer. 5-ALA is a precursor in the heme biosynthetic pathway of nucleated cells. It is metabolized by certain endogenous enzymes to protoporphyrinogen IX (PPIX), which is an endogenous photosensitizer. PPIX is an intermediate by-product in the heme biosynthetic pathway and it preferentially accumulates in tumor cells

due to changes in the activity of two main enzymes, porphobilinogen deaminase and ferrochelatase. Studies have shown a sensitivity of 95–100% for oral cancer diagnosis.

Hypericin fluorescence endoscope

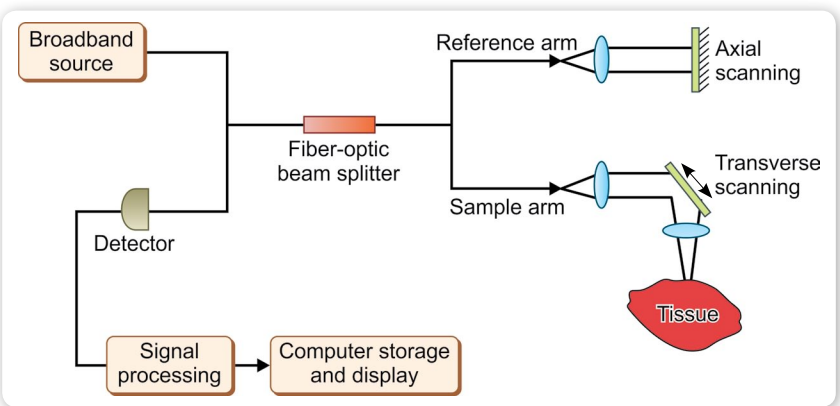


Representative images of white light (left) and hypericin image (right) of an oral lesion acquired using a fluorescence endoscopy system.

Principle: Hypericin is a plant-based photosensitizer that accumulates in abnormal cells including tumor cells. It can be used in fluorescence diagnostic imaging to facilitate guided biopsies, and also can provide visualization of tumor margins during surgical procedures. In both 5-ALA and hypericin fluorescence images, suspicious lesions displayed bright reddish color while normal surrounding mucosa exhibited blue color background.

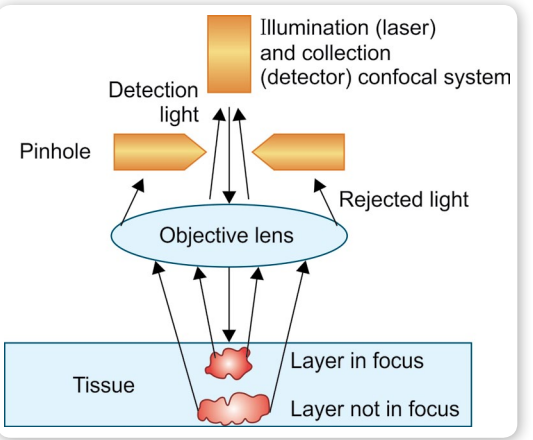
Source: Olivo M, Bhuvaneswari R, Keogh I. Advances in bio-optical imaging for the diagnosis of early oral cancer. Pharmaceutics.2011;3:354-78.

Optical Coherence Tomography (OCT)



Principle: Optical coherence tomography is a noninvasive optical imaging technique that produces cross-sectional images of tissue with a high spatial resolution of 10 to 20 μm. It uses broadband-limited coherence range laser light in near-infrared (NIR) region (770 to 1300 nm) to scan the topology of the tissue subsurface.

Laser confocal endomicroscope



The laser confocal endomicroscopy system consists of a low-powered laser (an Argon-ion laser that generates an excitation wavelength of 488 nm) that is focused onto a single point in a defined microscopic field of view, and the same lens is used as both the condenser and objective folding optical path. The point of illumination thus coincides with the point of detection within the specimen. Light emanating from that point is focused through a pinhole to a detector, and light emanating from outside the illuminated spot is rejected. The illumination and detection systems are in the same focal plane and are termed "confocal". Because confocal images depend on fluorescence, a fluorescent dye (contrast agent) is required to make objects visible. All detected signals from the illuminated spot are captured and measured. The gray-scale image created is an optical section representing one focal plane within the examined specimen. The image of a scanned region can be constructed and digitized by measuring the light returning to the detector from successive points. Series of confocal images within successive planes can be used to observe fine cellular or subcellular structures, and three-dimensional structures in the specimen can be imaged. In vivo imaging can be obtained by intravenously injected fluorescein and the dye acriflavine can be used for ex vivo imaging of SCC tissue.

Source: Olivo M, Bhuvaneswari R, Keogh I. Advances in bio-optical imaging for the diagnosis of early oral cancer. Pharmaceutics. 2011;3:354-78.

Table 10.1: Optical technologies in cancer sereening and detection

Modality	*Large filed of view*	*Using a contact prove*	*Resolution*	*Biology*	*Cost*	*Technology assessment*
Fluorescence spectroscopy	Yes	Yes	Subcellular	Measuring the biochemistry of tissue in the epithelium and stroma	Low	Evaluated in randomized clinical trials and commercialized for use in several organ sites
Reflectance spectroscopy	Yes	Yes	Subcellular	Measuring hemoglobin saturation in the stroma	Low	Technical efficacy studies underway and already commercialized
Elastic scattering of diffuse reflectance spectroscopy	No	Yes	10 μm	Measuring white light reflected back from chromatin in the cells of the epithelium	Low	Technical efficacy studies underway in many organ sites
Optical coherence tomorography	No	Yes	1–10 μm	Measuring the backscatter of light across the epithelium and stroma	High	Commercialized for the eye and under technical efficacy studies for other organ sites
In vivo confocal microscopy	No	Yes	1 μm	Measures nuclei in both the epithelium and stroma	High	Commercialized and technical efficacy studies by industry and several research groups underway

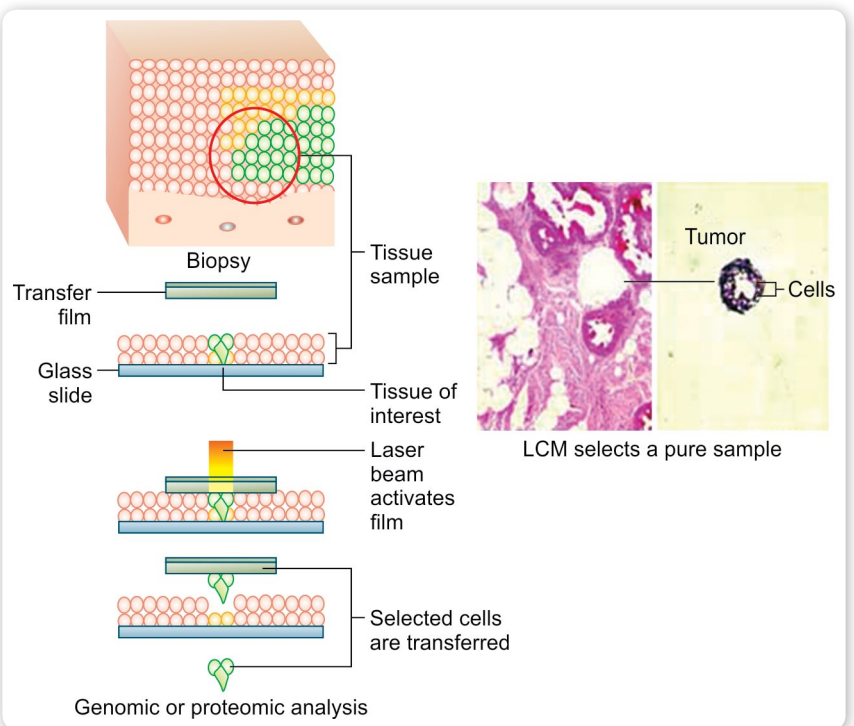
Source: Olivo M, Bhuvaneswari R, Keogh I. Advances in bio-optical imaging for the diagnosis of early oral cancer. Pharmaceutics 2011.3:354-78.

Potential future diagnostic aids

- Laser-induced fluorescence spectroscopy
- Light-induced fluorescence spectroscopy
- Elastic scattering spectroscopy
- Photoacoustic imaging
- Photon fluorescence
- Orthogonal polarization spectral (OPS) imaging
- Quantum dots
- Optical coherence tomography (OCT)
- Doppler OCT
- Nuclear magnetic resonance spectroscopy
- Chromoendoscopy
- Narrow band imaging (NBI)
- Immunophoto diagnostic techniques
- Differential path length spectroscopy
- 2 photon fluorescence 2nd harmonic generation Terahertz imaging.

Source: Scully c, Bagan JV, Hopper C, Epstein JB. Oral cancer: current and future diagnostic techniques. Am J Dent. 2008;21(4):199-209.

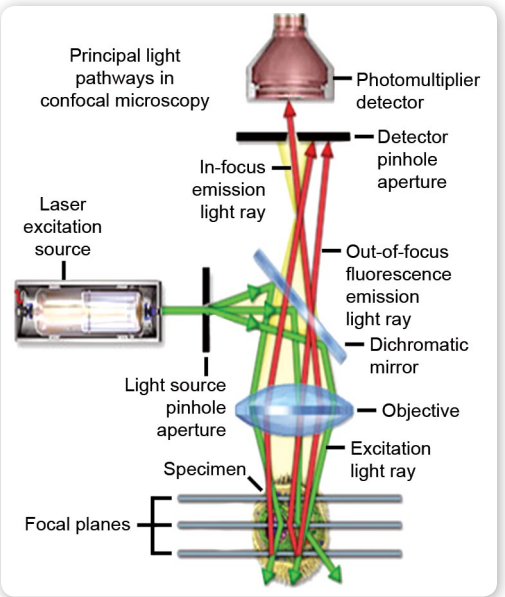
Other advanced diagnostic aids. Laser capture microdissection



Tumor markers in the saliva

1. Proteins of nuclear factor-kappa B dependent cytokines–(tumor necrosis factor-alpha, interleukin-1, interleukin-6, interleukin-8), basic fibroblast growth factor, Cyfra 21-1, cancer antigen-125 (CA-125), tissue polypeptide antigen, endothelin.
2. mRNA of interleukin-8, interleukin-1, DUSP1 (dual specificity phosphatase 1), H3F3A (H3 histone family 3A), OAZ (ornithin decarboxylase antizyme 1), S100P (S100 calcium binding protein P), SAT (spermidine/spermine N1- acetyltransferase EST).
3. Reactive nitrogen species (nitric oxide and nitrates), GST (glutathione S-transferase), SOD (superoxide dismutase) and 8-OHdG (8-hydroxyde-oxyguanosine).
4. MicroRNAs (miRNA) also have been found in human saliva and two miRNAs, miR-125a and miR200a, were found to be present in significantly lower levels in the saliva of OSCC patients than in healthy controls.

In vivo confocal microscope



In vivo confocal images show the characteristic features such as nuclear irregularity which is used to differentiate OSCC from normal oral mucosa. **Advantage:** Optical sectioning and high resolution imaging.

Principle: Confocal images depend on fluorescence. So, a fluorescent dye is required to make objects visible. All detected signals from the illuminated spot are captured and measured.

The image of a scanned region can be reconstructed and digitized by measuring the light returning to the detector from successive points. Series of confocal images within successive planes can be used to observe fine cellular or subcellular structures, and three-dimensional structures in the specimen.

CONFOCAL REFLECTANCE MICROSCOPY (CRM)

In vivo CRM is an optical tool to noninvasively image tissue with near histological resolution. Image contrast is determined by natural differences in refractive indices of organelles and other subcellular structures within the tissues. CRM differs from a conventional microscope as it uses a laser to illuminate a small spot within tissue. Light that is backscattered from the tissue is captured through an aperture, which matches the size of the illuminated spot placed in front of the detector.

DIAGNOSTIC TESTS

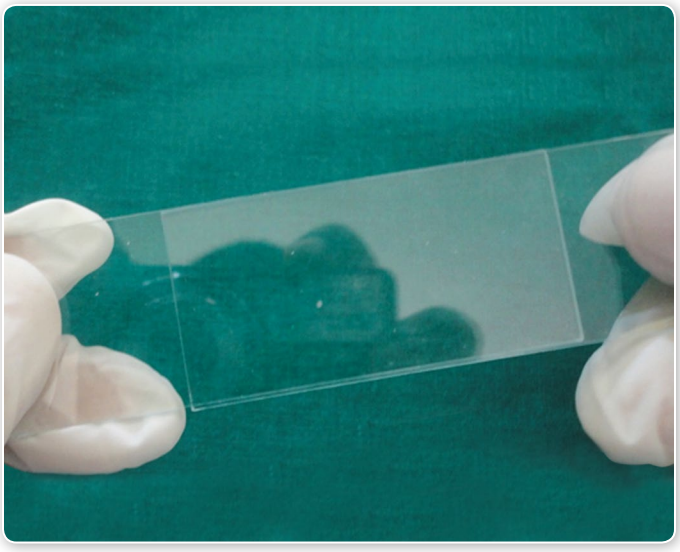
Exfoliative Cytology



Technique of exfoliative cytology using of the oral mucosa using icecream stick.



Picture demonstrating spreading of sample on a slide.

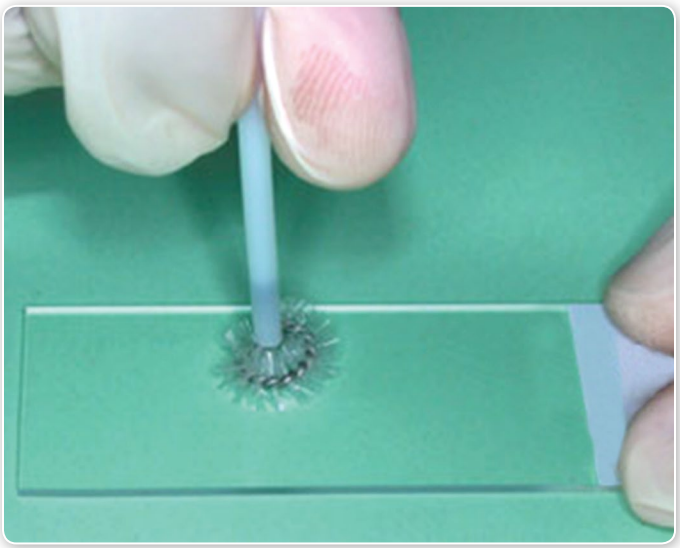


Picture demonstrating smearing of sample on a slide.

Brush Biopsy



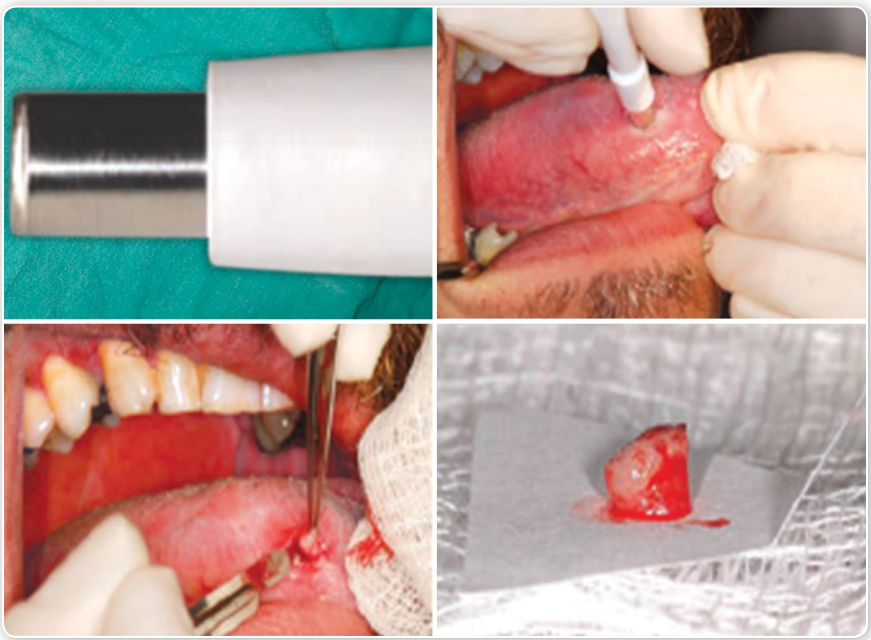
The head of the brush is rotated clockwise with firm pressure till the bleeding points appear.



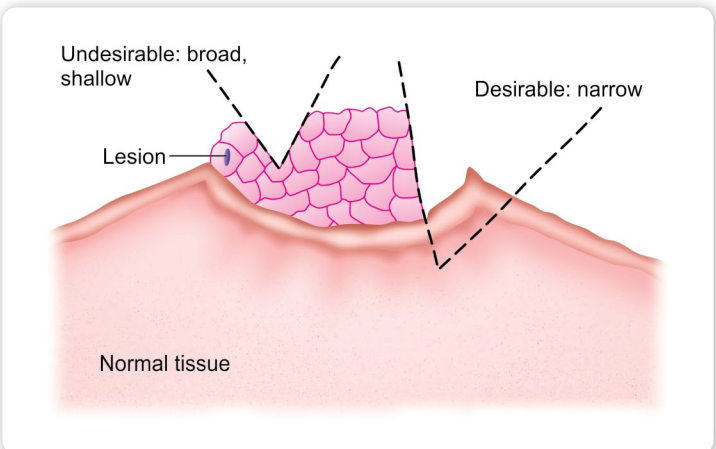
The brush is rotated anticlockwise by appliying firm pressure on the slide.

BIOPSY

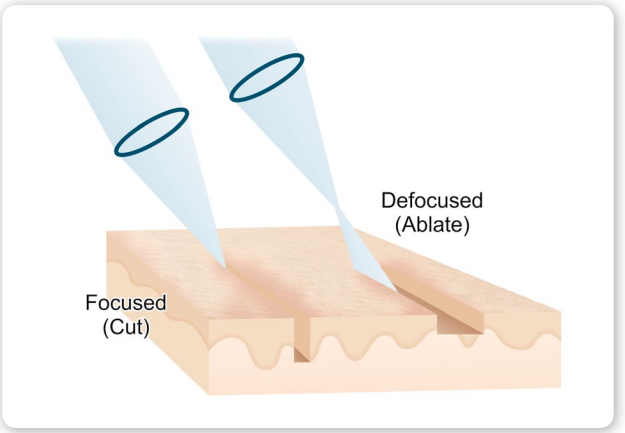
Punch Biopsy



Scalpel Biopsy



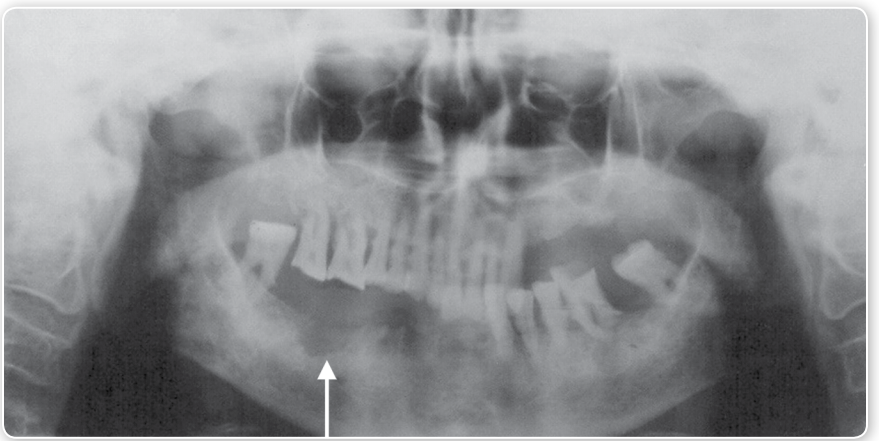
Laser Beam Biopsy



Histopathological examination of the biopsy specimen is the gold standard in the diagnosis of the oral cancer.

IMAGING

Orthopantomograph (OPG)



Irregular radiolucency (white arrow) involving the body of the mandible at 45-46 region.

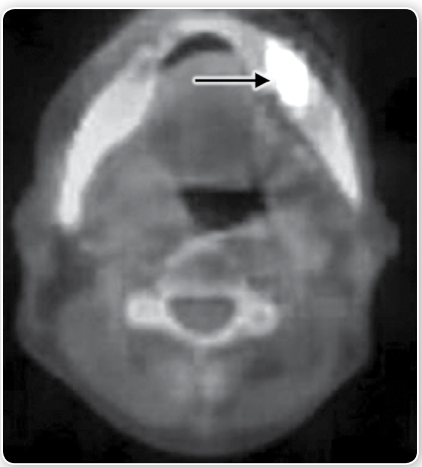
Computed Tomography



Axial contrast enhanced CT image demonstrates an enhancing soft tissue mass (white arrows) along the buccal mucosa, a finding consistent with SCC. Erosion of the adjacent maxilla (black arrow) also is seen.

Source: Trotta Brian M. et al. Oral cavity and oropharyngeal squamous cell cancer: key imaging findings for staging and treatment planning. Radiographics. 2011; 31:339–54.

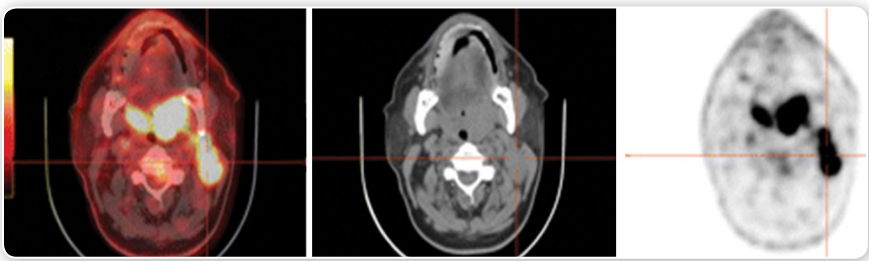
Bone Scintigraphy with Single Photon Emission CT (SPECT)



Transverse coregistered SPECT/CT scan showing increase uptake of Technetium-99m 3,3-diphosphono-1,2-propanedicarboxylic-acid (^{99m}Tc DPD) (arrow), a finding that is suggestive of bone invasion. Commonly used tracers are in SPECT—^{123}I and ^{99m}Tc derivatives.

Source: Goerres GW, et al. Bone invasion in patients with oral cavity cancer: comparison of conventional CT with PET/CT and SPECT/CT. Radiology. 2005; 237:281–7. *Abbreviation* [^{18}F]-fluoro-2-deoxy-glucose (FDG); positron emission tomography (PET scan).

[18F]-fluoro-2-deoxy-glucose (FDG) positron emission tomography (PET) Scan



The malignant lesion presents as a glow due to increase uptake of F FDG.

Principle: Monitors the glucose metabolism.

Source: Sch¨oder H, Fury M, Lee N, Kraus D. PET monitoring of therapy response in head and neck squamous cell carcinoma. J Nucl Med. 2009; 50:74S–88S.

PET IMT: L-3-^{123}I-Iodo-α-methyltyrosine (^{123}I-IMT) is a radiolabeled amino acid. Tumor evaluation, i.e. detection, grading and therapy monitoring can be obtained by quantitative assessment of protein synthesis rate. This can be obtained by using radiolabeled amino acids as a radiolabeled molecular imaging probe.

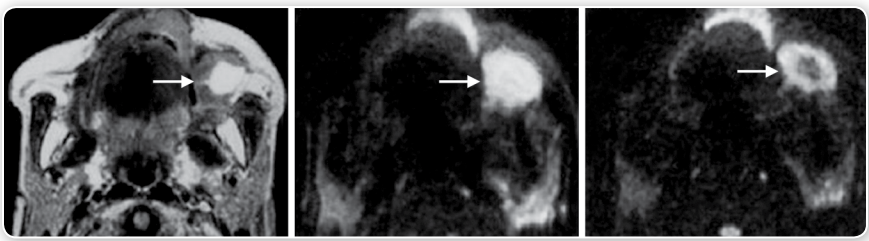
Gene reporter imaging: It is used to detect nucleosides metabolism. Nucleosides or nucleoside analogs can be phosphorylated intracellularly by specific kinases and, ultimately, they can be incorporated into DNA. Thymidine kinase 1 (tk1) is a nuclear label that shows an S-phase dependant expression. The intracellular accumulation of labeled nucleosides that are substrates for TK1 reflects DNA synthesis and thus tumor proliferation. ^{131}I and ^{124}I labeled 2-arabino-fluoro-5-iodo-2-deoxyuridine (FIAU) has been used successfully as nucleoside analog for tumor proliferation detection.

Hypoxia imaging: Hypoxia occur when there is insufficient O_2 to support metabolism. Most hypoxia markers contain a nitroimidazole moiety as a reactive chemical species. Nitroimidazoles can be used as probes to detect hypoxia as they are reduced intracellularly in all cells, but in hypoxic tissue they undergo further reduction to more reactive products which bind to cell components and are finally trapped in the hypoxic tissue. ^{99m}Tc-O-propylene-amine-oxime (^{99m}Tc-pano or BMS-181321) was validated as a proper hypoxia imaging agent in hypoxic myocardium, acutely ischemic brain and solid tumors. BMS-194796 and ^{99m}Tc-HL91 have also been designed as marker for imaging hypoxia, however, none of these three probes has been commercially available. Iodine-123 labeled iodoazomycin arabinoside (IAZA) has been validated in animal model in the preclinical phase, but no clinical studies with this agent have been reported so far.

Cell Labeling: Avid In-111 used for labeling white blood cells and platelets for imaging inflammatory processes and thrombi. ^{99m}Tc-HMPAO is currently used in brain perfusion imaging.

Khalil MM, Tremoleda JL, Bayomy TB, Gsell W. Molecular SPECT imaging: an overview; Int JMOL Imaging 2011:7.9625

Diffusion-Weighted Magnetic Resonance Imaging (DW-MRI)



Representative case of a well-differentiated squamous cell carcinoma of the maxilla

(A) Axial spin–spin relaxation time-weighted image of a metastatic buccinator node (arrow) that shows a large, hyperintense necrotic area. **(B)** Axial diffusion-weighted echo-planar MR image at b factor of 500 s/mm^2, the metastatic node appears hyperintense (arrow). **(C)** Axial diffusion-weighted echo-planar MR image at b factor of 1000 s/mm^2, the metastatic node exhibits a central hypointense area (arrow) corresponding to the partially necrotic portion of the node.

Principle: In the cellular environment the water molecule may have free or restricted diffusion. The free water molecules are in constant random motion, called as Brownian motion. The motion of water molecules within the cellular microenvironment is impeded by their interaction with cellular compartments, including the cell wall and intracellular organelles. Which means the restriction in the diffusion of water molecules is directly proportional to the degree of cellularity of the tissue. This restricted diffusion is observed primarily in malignancies, hypercellular metastases, and fibrosis, which contain a greater number of cells with intact cell walls compared to healthy tissue. In contrast, in a microenvironment with fewer cells and a defective cell membrane (e.g. the necrotic center of a large mass), water molecules are able to move freely, i.e. diffusion is less restricted. The magnitude of this motion is characterized by its apparent diffusion coefficient (ADC) values.

The chief advantage is does not require administration of a contrast agent and thus, is completely noninvasive.

It can be used in:

- Characterization of head and neck tumors,
- Imaging in cervical lymph nodes,
- Differentiation between the viable and necrotic parts of malignant tumors,
- Differentiation between recurrent/residual tumors and post-treatment changes,
- Prediction and monitoring early treatment response.

Source: Chawla S, Kim S, Wang S, Poptani H. Diffusion-weighted imaging in head and neck cancers. Future Oncol. 2009; 5(7): 959–75.

Dynamic Contrast Enhanced MRI

The technique of dynamic contrast enhanced (DCE) magnetic resonance imaging (MRI), in which multiphase MRI scans are taken following the intravenous injection of a contrast agent.

The contrast medium used for this technique is assumed to be predominantly confined to the vascular space, which thus provides the valuable information about perfusion, such as the blood volume (BV), blood flow (BF), and transit time. This process of new vascularization or angiogenesis is a signature of neoplasms and one of the principal potential targets for quantitative imaging.

These techniques provide information regarding tumor permeability and perfusion, extracellular space, and tumor oxygenation in addition to tumor morphology. The ability to quantify angiogenesis and changes in oxygenation particularly in this era of novel biologically targeted therapy is essential.

Source: Chikui T, et al. The principal of dynamic contrast enhanced MRI, the method of pharmacokinetic analysis, and its application in the head and neck region Int J Dent. 2012; 2012: Article ID 480659.

Blood oxygenation level–dependent (BOLD)-MRI: This techniqhe is Used in the assessment of biological changes in response to both conventional cytotoxic and other novel therapeutic agents. It uses the biological property of deoxyhemoglobin shows higher relaxivity compared to oxyhemoglobin. These measurements reflect blood volume, perfusion, intrinsic composition of tissues and level of tissue oxygenation.

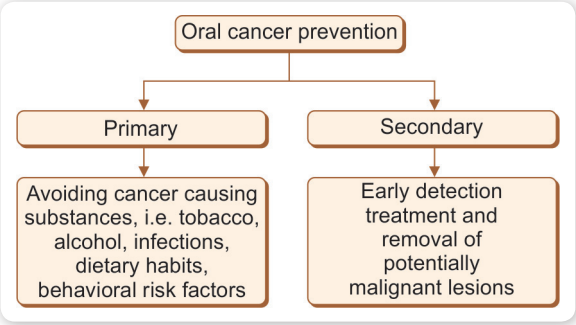
Source: Li SP, Padhani AR, Makris A. Dynamic contrast-enhanced magnetic resonance imaging and blood oxygenation level-dependent magnetic resonance imaging for the assessment of changes in tumor biology with treatment. J Natl Cancer Inst Monogr. 2011;43:103–7.

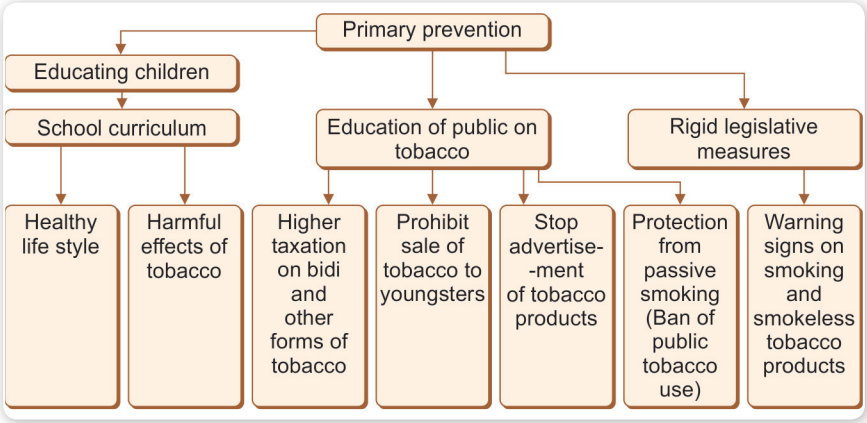
Hydrogen (1H) Magnetic resonance spectroscopy: It can examine metabolic changes in neoplastic tissues. It is based on the detection of elevated choline levels, which is involved in cell membrane synthesis, which is a marker of tumor activity, i.e. tumor grade and proliferation index. Decreases in choline and increases in lactate can indicate therapy response.

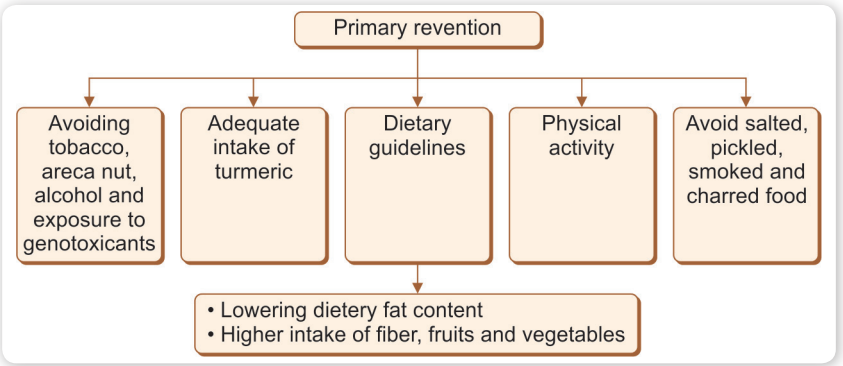
Source: Li SP, Padhani AR, Makris A. Dynamic contrast-enhanced magnetic resonance imaging and blood oxygenation level-dependent magnetic resonance imaging for the assessment of changes in tumor biology with treatment. J Natl Cancer Inst Monogr. 2011;43:103–7.

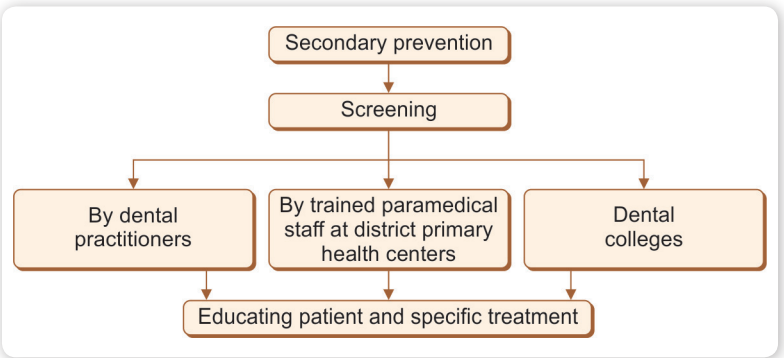
Chapter 11

Prevention









Diet and Cancer Prevention

Retinoids: Transretinoic acid, are inhibitors of substances specific to tumoral promotion. Powerful antioxidants, protecting cellular lipids from oxidation, particularly the cell membrane lipids, sequester free radicals and nascent oxygen, prevent cancer by activation genes involved in cellular differentiation processes. They interfere with the ornithine-decarboxylase enzyme, responsible for polyamine synthesis thus controlling cell division.

Important in the synthesis of glycoproteins such as galactose and manose, which are cellular adhesion and growth mediators as well as hormonal receptors. Reduced cellular adhesion characterized by a loss of cellular adhesion and a greater invasive and metastasising ability.

They are powerful stimulators of the immune system, i.e. T lymphocytes, reinforcing the natural defence mechanisms against tumoral invasion.

Alpha-Tocopherol (Vitamin E): It has been shown to be effective in inhibiting tumoral promotion.

Vitamin C: Antioxidant and help to prevent oxidative stress.

Iron can generate the reactive oxygen species including hydroxyl radicals which can cause DNA mutation and limiting nutrient to the growth and replication of cancer cells in the human body.

Copper has been implicated in the activation of several organic peroxides and making them more carcinogenic.

Zinc is an anti-carcinogenic role by stabilizing the structure of DNA, RNA, and ribosome. Essential to the functions of several transcription factors and regulate gene transcription. Protects against free radical injury and may affect immune response.

Selenium inhibits tumor initiation or activation processes,

- Associated with the functioning of the glutathione peroxidase enzyme helping in regeneration of the glutathione molecule,
- Elimination of hydroperoxide and hydrogen peroxide,
- Reduce the metabolism of the carcinogens,
- Protecting the DNA or facilitating DNA repair mechanisms.

Manganese is a component of the antioxidant enzyme superoxide dismutase (SOD). Manganese and manganese superoxide dismutase play an important role in the differentiating cells.

Curcumin (diferuloylmethane) is a polyphenol derived from the turmeric (Curcuma longa) plant.

- Inhibiting lipid peroxidation, free radical-scavenging activity.
- Down regulates the iNOS activity in macrophages, thus reducing the amount of reactive oxygen species (ROS) generated in response to oxidative stress.
- Suppress the activation of NF-κB. Increased NF-κBis associated with various steps in the development of malignancy such as expression of anti-apoptotic genes, angiogenesis, tumor promotion and metastasis.

Cruciferous plants cauliflower, broccoli and cabbage are important source of isothiocyanate, which interferes in the metabolism of the nitrosamines.

Garlic- Sulphite is a powerful inhibitor of cytochrome p450. Allyl-2-propenyl radicals—inhibit the formation of malignant tumors induced by different initiator molecules.

Green tea polyphenols, i.e. phenolic acids and the flavonoids, both have antioxidant properties—help eliminate oxygen-free radicals and inhibit nitration reactions.

Omega-3 fatty acids resulting in an altered membrane composition and function. Cell membranes with increased fluidity, an elevated unsaturation index, enhanced transport capabilities that results in accumulation of selective anti-cancer agents, increased activity of selected drug activating enzymes, and alteration of signaling pathways important for cancer progression.

Table 11.1: Dietary flavonoids and their sources

Subclass	*Dietary flavonoids*	*Common food sources*
Anthocyanidins	Cyanidin, delphinidin, malvidin, pelargonidin peonidin, petunidin	Red, blue, and purple berries; red and purple grapes: red wine
Flavanols	**Monomers** (catechins): Catechin, epicatechin gallate, epigallocatechin-3-gallate Dimers and polymers: theaflavins, thearubigins, proanthocyanidins	Catechins in teas (green and white); chocolate, grapes, berries, apples; theaflavins thearubigins in teas (black and oolong); proanthocyanidins in apples, berries, grapes, red wine
Flavanones	Hesperetin, naringenin, eriodictyol	Citrus fruits and juices, e.g. oranges, grapefruits, lemons
Flavonols	Quercetin, kaempferol, myricetin isorhamnetin	Yellow-onions, scallions, kale, broccoli, apples, berries, teas
Flavones	Apigenin, luteolin	Parsley, thyme, celery, hot peppers
Isoflavones	Daidzein, genistein, glycitein	Soybeans, soy foods, legumes

Source: Dashwood RH. Frontiers in polyphenols and cancer prevention. J Nutr. 2007;137: 267S–9S.

Chapter 12

Treatment

ORAL LEUKOPLAKIA

Available nonsurgical treatment list:

a. Beta-carotene—(360 mg/week)
b. Lycopene 4–8 mg/day
c. L-ascorbic acid (Vitamin C)140 mg/day
d. Alpha-tocopherol (Vitamin E)—The recommended daily limit rates are 400-800 IU/day
e. Combination of a,c,d
f. Systemic vitamin A—200,000 IU/week
g. Topical isotretinoin—0.05% to 1%
h. Fenretinide-Fenretinide (4-HPR) or N-(4-hydroxyphenyl) retinamide—200 mg/day for 3 months
i. Bleomycin-cytotoxic antibiotic—0.5%/day for 12 to 15 days or 1%/day for 14 days
j. Photodynamic therapy (PDT).

In case of all the potentially malignant lesions biopsy is mandatory to rule out dysplasia. In case of dysplasia, surgical removal of the lesion is indicated. For all the cases educating patient for the cessation of the habit and regular long-term follow-up is recommended.

ORAL SUBMUCOUS FIBROSIS

Treatment Details

Micronutrients and minerals—Vitamin A, B complex, C, D and E, iron, copper, calcium, zinc, magnesium, selenium.

a. Milk from immunized cows—45 g milk powder twice a day for 3 months.
b. Lycopene—8 mg twice a day for 2 months.
c. Pentoxifylline—400 mg 3 times a day for 7 months.

d. Interferon gamma—Intralesional injection of interferon gamma (0.01–10.0 U/mL) 3 times a day for 6 months.
e. Steroids—Submucosal injections twice a week in multiple sites for 3 months.
f. Steroids—Topical for 3 months.
g. Hyalase + dexamethasone
h. Placental extracts—Local injection of placental extract 2 mL every week for 12 weeks.
i. Turmeric—Alcoholic extracts of turmeric (3 g), turmeric oil (600 mg), turmeric oleoresin (600 mg) daily for 3 months.
j. Chymotrypsin hyaluronidase and dexamethasone—Chymotripsin (5000 IU), hyaluronidase (1500 IU) and dexamethasone (4 mg), twice weekly submucosal injections for 10 weeks.

Fibrosis in oral submucous fibrosis cannot be reversed. The early form of the disease can be treated by drugs for symptomatic relief, but, advanced cases needs surgical excision of the fibrotic bands. Reconstruction can be done with grafts such as split thickness skin grafting, bilateral nasolabial flaps, palatal island flaps, tongue flaps, buccal fat pad graft and temporalis muscle flap graft. Alternative procedures, such as insertion of an oral stent, physiotherapy, local heat therapy, mouth exercises using acrylic carrots and ice cream sticks, have been tried with variable rates of success.

Any suspicion of dysplasia histopathological confirmation is mandatory. In most cases, depending on the stage of disease and extent of oral involvement, therapy consisting of a combination of the above-mentioned drugs and surgery might be useful.

Auluck A, Rosin MP, Zhang *L, Sumanth KN.* Oral submucous fibrosis, a clinically benign but potentially malignant disease: Report of 3 cases and review of the literature. I Can Dent Assoc. 2008;74(8):735-40.

ORAL LICHEN PLANUS

Asymptomatic Nonulcerative Lichen Planus

Explanation of the nature of the condition, including its aetiology, clinical features, treatment, follow up and prognosis and reassurance. Advice on avoidance of risk factors such as tobacco and alcohol. Empirical dietary advice regarding intake of fresh fruit and vegetables.

Symptomatic Nonulcerative Lichen Planus-Compensatory

Symptomatic relief using topical anesthetic and/or barrier agents such as Benzydamine hydrochloride (0.15%) spray or mouthrinse, 2% lidocaine gel to painful areas. Antiseptic mouthwashes such as chlorhexidine gluconate. If possible obviate any provoking factors, e.g. toothpastes, medications, amalgam restorations.

Atrophic/Ulcerative Oral Lichen Planus

Topical corticosteroid preparations:

Soluble prednisolone tablets, 5 mg dissolved in 15 mL of water and used as a mouthrinse 3–4 times daily.

Betamethasone sodium phosphate (500 mcg dissolved in 10–15 mL of water) used as a mouthrinse up to 4 times daily.

Fluticasone propionate spray (50 mcg per puff), directed to affected areas up to 3–4 times daily.

Beclomethasone spray (100 mcg per puff), sprayed 3–4 times daily on affected sites.

Clobetasol ointment (0.05%) applied to painful areas 3–4 times daily.

Fluticasone cream (0.05%) applied to painful sites 3–4 times daily.

Appropriate topical antifungal in clinical signs of candidiasis.

Severe, Symptomatic Atrophic/Ulcerative Oral Lichen Planus, Unresponsive to Topical

Measures systemic steroids [prednisolone, deflazacort], short reducing dose followed by maintenance with topical corticosteroids + antifungals if appropriate.

Recalcitrant Oral Lichen Planus

Low dose, short-term corticosteroids, appropriate surveillance for hypertension, diabetes and bone prophylaxis—DEXA scan, calcium +D3 supplements/bisphosphonates as appropriate.

Azathioprine + corticosteroids, with prior assessment of TPMT levels and appropriate monitoring.

Topical cyclosposine [100 mg/mL] as a mouthwash twice daily [consider checking blood levels].

Topical tacrolimus. Protopic 0.03%; 0.1%; monitoring of blood levels of tacrolimus is no longer considered necessary.

Mycophenolate mofetil and methotrexate requires further study.

Desquamative Gingivitis

Intensive oral hygiene program occlusive corticosteroid therapy [fluocinolone acetonide]

Long-term review and avoidance of risk factor such as tobacco and alcohol in must in all patients. Titrate the drug dosage and duration according to patient needs in all cases. In case any suspicion of dysplasia histopathological confirmation is mandatory.

Source: Guidelines for the management of oral lichen planus in secondary care. October 2010.

NONPHARMACOLOGICAL MODALITIES

PUVA Therapy

Photochemotherapy with 8-methoxypsoralen and long wave ultraviolet light (PUVA).

Methoxypsoralen is given orally, followed by administration of 2 hours of UV radiation intraorally in the affected sites. It has been successfully used in the treatment of severe cases of OLP.

Photodynamic Therapy (PDT)

Photosensitizing compound like methylene blue, activated at a specific wavelength of laser light. This destroys the targeted cell via strong oxidizers, causing cellular damage, membrane lysis, and protein inactivation.

Laser Therapy

It is used in patients with painful erosive OLP and are unresponsive to topical superpotent corticosteroids. Different types of laser such as 980-nm diode laser, CO_2 laser evaporation, biostimulation with a pulsed diode laser using 904-nm pulsed infrared rays and low-dose excimer 308-nm laser with UV-B rays have been tried. The few studies show good response, but their effectiveness is yet to be proven.

No therapy for OLP is completely curative.

Source: Lavanya N, Jayanthi P, Rao UK, Ranganathan K. Oral lichen planus: an update on pathogenesis and treatment. J Oral Maxillofac Pathol. 2011;15(2):127–32.

Treatment for Oral Cancer

(Staging is based on TNM staging)

Stage 0 (Carcinoma in Situ)

Surgical removal of lesion with the small margin of normal tissue followed by regular follow-up. In case of recurrence radiotherapy may be required.

Stages I and II

Most patients with stage I or II oral cancer can be successfully treated with either surgery or radiation therapy. Chemotherapy (chemo) may be combined with radiation, especially to treat any cancer left after surgery.

Stages III and IV

More advanced oral cancers generally require a combination of either surgery and radiation, or radiation and chemo, or a combination of all three. The choice of treatment is influenced by where the cancer is, how much it has spread, the expected side effects, and the patient's current health status.

Recurrent Oral Cancer

Recurrence can be local (in or near the same place it started), regional (in nearby lymph nodes), or distant (spread to bone or organs such as the lungs). Treatment options for recurrent cancers depend on the location and size of the cancer, what treatments have already been used, and on the person's general health.

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